# FINAL REPORT

## Evaluation of NIH Implementation of Section 491 of the Public Health Service Act, Mandating a Program of Protection for Research Subjects

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## PREFACE

This independent evaluation report was written under National Institutes of Health Contract No. N01-OD-2-2109, which also supported study design, data collection, and data analysis. A separate volume of technical appendices contains the five questionnaires administered for the evaluation, a glossary of terms, a list of references cited in the report, and assorted methodological materials and technical notes.

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## EXECUTIVE SUMMARY

This report documents findings from an NIH-sponsored evaluation of the implementation of Section 491 of the Public Health Service Act. For purposes of the evaluation, the study universe was defined as the 491 Institutional Review Boards (IRBs) that in 1995 operated with multiple project assurances (MPA) issued under 45CFR46, and which had conducted more than 10 initial reviews of human subjects research protocols in the previous year.

The overarching general conclusion of the evaluation is that the IRB-based human subjects protection program has been implemented consistent with the regulations. Despite some perhaps unforeseen accommodations to the rising volume of human subjects research, the IRB system continues to provide an adequate level of protection at a reasonable cost. Nonetheless, there is a near-unanimous view that human subjects protection can be further improved by honing IRB structures and procedures and providing increased education and training. Simply put, the program is working well and not in need of major adjustments, at least according to the nationally representative sample of more than 2,000 human subjects researchers and IRB chairpersons, members, administrators and institution officials who participated in the evaluation.

**Chapter I**, **Introduction**, provides a brief overview of the human subjects protection regulations (45CFR46), the mechanisms at the local and federal levels established to promote adequate protection, prior research and evaluations, and the design of the present study. This sets the stage for a presentation of the many specific findings that led to the general conclusions stated above, including details about the volume of protocols and characteristics of research overseen by IRBs, their personnel and practices, the amount and reasonableness of effort expended, the adequacy of protection, and suggestions for enhancing human subjects protection.

As described in **Chapter II**, **IRB Workload: Annual Volume of Reviews and Charcteristics of Investigators and Protcols**, IRBs are defined in part by the amount and types of human subjects research they review and oversee. Since the last national study, the volume of human subjects research has increased dramatically, leading some observers to conclude that rising workloads of protocols have led to overstressed IRBs. In a recent record year, the IRBs in the study universe conducted an estimated 284,000 reviews (95% C.I.), including 105,000 initial reviews (exempt, expedited, and full board) that accounted for 37 percent of the total, 116,000 continuing/annual reviews (41 percent) and 63,000 reviews of amendments to approved protocols (22 percent). The following are key findings about the IRB review workload in the most recently completed record year, which was typically reported as beginning in 1995:

- The yearly volume of 284,000 initial, continuing/annual, and amendment reviews was distributed quite unevenly among IRBs -- perhaps the most distinguishing feature of the IRB landscape. In this regard, the high peaks are the 10 percent of IRBs (in the highest volume decile) with about 105,100 reviews annually, accounting for 37 percent of the national total. Together, the 246 high-volume IRBs conducted 88 percent of the yearly total.

- Overall, the 105,000 initial reviews conducted annually were split between full-board review (58 percent) and a combination of exempt (17 percent) and expedited reviews (25 percent). Multicenter protocols represented 30 percent of the total submissions for initial review.

- Seventy-two percent of investigators reported they had first conducted research with human subjects prior to 1990, and 33 percent said they had first done so prior to 1980. Seventeen percent had one year or less experience.

- When investigators described the kinds of research conducted under the protocol designated in their questionnaires, clinical research (51 percent), behavioral research (14 percent), and biomedical research (9 percent) emerged as the most frequently mentioned types, with the remainder (26 percent)

spread across educational research, social sciences research, and other kinds. Investigators at high-volume IRBs reported clinical and biomedical research combined as 69 percent of the total, compared to 55 percent at low-volume IRBs.[1]

- According to chairs, NIH (25 percent) and industry (25 percent) were the leading sources of funding for protocols reviewed by their IRB, together accounting for about one-half of protocols that were implemented. Institution funds (11 percent) and pre-existing resources (17 percent), which are both internal sources, and a combination of other external sources (besides NIH and industry), including federal, philanthropic and state funds, together supported the remainder of funded protocols (22 percent).

- Nearly half (46 percent) of investigators indicated that some subjects (experimental or control) were seeking or receiving clinical care for the mental or physical condition under study. With regard to the health conditions of subjects who were seeking or receiving clinical care, almost one-half of those investigators (47 percent) said their subjects had very serious conditions; within that group, one in three protocols (or 16 percent of all protocols) had subjects with either a terminal condition, medical emergency, or attenuated ability to comprehend.

As described in **Chapter III**, **IRB Personnel and Policy/Practices**, IRBs rely on the direct participation of thousands of people to carry out human subjects protection. This requirement is strongest for high-volume IRBs, which have adapted to their larger workloads both by adding personnel and making adjustments in practices. Thus, the number of members and administrative staff, frequency of full board meetings, and duration of meetings were all greater for high-volume IRBs than for their low-volume counterparts. The following are additional findings about the human resource and policy aspects of IRBs:

- IRB personnel are predominantly white and well-educated, with chairs and members more likely to be male, and administrators more likely to be female. The chairs of IRBs in the present study brought considerable experience to the position.[2] They had a mean of 5.2 years serving as chairs of the study IRBs and a range of total IRB experience of less than 1 year to more than 32 years. Regarding total experience on any IRB, as chair or member, the mean for chairs at high-volume IRBs was 10.4 years, compared with 8.8 years of service for low-volume chairs.

- According to OPRR records updated in the summer of 1995, the 491 study IRBs had 6,923 members, with membership ranging in size from 5 (the minimum mandated by law) to 44 members. The mean number of members for IRBs in the lowest volume decile was 10.5, compared to a mean of 19.7 members in the highest volume decile.

- Administrators indicated they had staffed, in any capacity, the specific IRB or any other IRB for a mean of 7.2 years, with 29 years being the maximum reported. In terms of the total number of IRBs overseen by an administrator, the vast majority (84 percent) were responsible for a single IRB, and 15 percent had 2 to 6 IRBs.

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[1]Clinical/biomedical research includes clinical research, biomedical science, and epidemiology. Behavioral/Social research includes social science, behavioral science, educational research, and health services research.

[2]There were fewer individual chairs (478) than study IRBs (491), because 13 individuals chaired more than one IRB.

- Administrators reported that 498,000 person-hours were expended in a recent year on IRB activities by administrative support staff working under the supervision of the IRB administrator. Administrative staff distribution is very uneven across IRB volume deciles;15 percent and 100 percent of the lowest and highest decile IRBs have administrative staff, respectively.

- For every exempt and expeditable research category, chairs indicated there were substantial proportions of IRBs -- ranging between 25 and 77 percent, depending on IRB volume and research category -- that chose as standard practice some form of review that was more rigorous than specified by the regulations.

- Based on chairs' reports for 1995, a total of 4,834 full board meetings were held by IRBs in the study, with a range for individual IRBs extending from 1 to 50 IRB meetings. The mean annual total of full board meeting time ranged from 8.6 hours for IRBs in the lowest volume decile to 50.2 hours for those in the highest volume decile.

Based on factual and opinion data gathered for the study, **Chapter IV**, **Reasonable Burden, Sufficient Effort**, describes the person-time expended on IRBs, and then explores the sufficiency and reasonableness of that effort by examining inter-IRB variations. Are human subjects protection requirements too much of a burden (as many argue), or do they allow institutions to expend too little effort (as others claim)?

- In a recent record year, approximately 1.7 million person-hours were devoted to running the 491 IRBs in the study universe (95% C.I.). A breakdown of the total annual person-time reveals that, in roughly equal proportions, members (516,000 person-hours), administrative staff (498,000 person-hours), and administrators (472,000 person-hours) together accounted for 89 percent of total effort. In addition, chairs supplied 7 percent of the effort (122,000 person-hours), while institution officials contributed 4 percent (62,000 person-hours).

- There was a strong positive correlation between workload size (indicated by annual volume of initial reviews) and the number of hours of chair effort per year; chairs of IRBs in the highest volume decile devoted a mean of 378 hours per year, compared to 61 hours for chairs of IRBs in the lowest volume decile. On average, individual members at the highest and lowest volume IRBs spent 108 and 28 hours per year, respectively. For the highest volume IRBs, the mean number of administrator-hours per month was 122, compared to a mean of 12 hours per month for the lowest volume IRBs.

- Administrative staff support totaled just under 110,000 person-hours for IRBs in the highest volume decile (or an average per IRB of about 2,245 hours per year engaged in IRB work), while the lowest volume IRBs had a total of 2,490 hours per year of administrative staff effort and an average per IRB of 51.

- Almost two-thirds of investigators reported they had spent 8 or fewer hours (with a median of 5 hours) preparing for initial IRB review and responding to any IRB questions and/or requests for modifications to the protocol they were asked to report on. The mean person-hours expended on full board initial review by investigators was twice as much as the average amount of investigator effort spent per expedited review, 13.9 hours vs. 7.4 hours, respectively.

- The analysis revealed that irrespective of type of review -- initial, continuing/ annual, or amendments -- the pattern of differences between high- and low-volume IRBs was consistent. Typically, the IRBs in the lowest volume decile spent about two times more person-time per review than IRBs with the highest workloads.

- Based on data provided by IRB chairs, the mean number of meeting minutes per full board and expedited initial review was 21.3 and 3.9, respectively, for IRBs in the low volume decile. Thus, the average meeting time per full-board initial review at the lowest volume decile IRB was seven times longer than for IRBs in the highest volume decile.

- Equally high percentages of chairs and members (87 percent and 84 percent, respectively) agreed with the statement that "This IRB runs with reasonable efficiency." Although a majority of investigators (64 percent) also agreed with the statement, they were less likely than chairs and members to do so.

**Chapter V**, **Adequacy of Protection**, presents findings on the adequacy of human subjects protection relative to the 491 MPA IRBs in the study universe. These findings are based on opinion data/ratings and factual reports provided by more than 2,000 individuals who are intimately involved in carrying out institution-level human subjects protection -- albeit from somewhat different perspectives:

- Chairs and members were nearly unanimous in agreeing with the statement, "This IRB protects the rights and welfare of human subjects." With regard to investigators, 83 percent agreed with that statement, including 55 percent who were in strong agreement.

- Thirty-nine percent of investigators reported that initial review had either considerably or somewhat strengthened the human subjects protection aspect of their protocol. When asked to rate various influences on the adequacy of human subjects protection at their institution in terms of estimated impact, a substantially greater percentage of chairs than investigators rated the impact of IRB actions as high, at 82 percent to 58 percent, respectively.

- While nearly equal majorities of chairs and members (56 and 55 percent, respectively) agreed with the statement that the scientific quality of research done on human subjects is improved by IRB review, a substantially smaller 37 percent of investigators were in similar agreement.

- Sixty percent of chairs reported that "language too technical or otherwise unclear" -- the most common consent form concern -- occurred often.

- The likelihood of an investigator modifying his/her protocol, 43 percent overall, was substantially lower (24 percent) for protocols undergoing expedited initial review than for protocols receiving full board initial review (49 percent).

- "Failure to obtain IRB approval to initiate a study" was the form of investigator non-compliance cited most frequently by chairs (33 percent).

**Chapter VI**, **Alternatives at the Local and Federal Levels**, offers alternatives for IRB procedures and structures, education and training, additional resources and a miscellaneous collection of other suggestions, as provided by IRB chairs, members, administrators, institution officials, and investigators.

**Chapter VII**, **The IRB System: Where It's Been, Where It's Going**, contains a discussion of the IRB system in terms of its past and future. While the current study offers a nationally representative portrait of the IRB system in the mid-1990s, it does not directly address how the system has changed (or not changed) over time; this chapter examines prior research in relation to the present study, and recommendations in the literature for human subjects protection in the future.

# CHAPTER I
# INTRODUCTION

Since the 1960s, significant advances in protecting the rights and welfare of human subjects in biomedical and behavioral research have occurred. A key factor in this process has been the hundreds of Institutional Review Boards (IRBs) established at organizations throughout the United States engaged in federally-funded human subjects research. With roots in the risk protection principles of the Hippocratic Oath and more recent ethical doctrines like the Nuremberg Code, the IRB system currently oversees tens of thousands of research studies conducted by federally-funded institutions. The massive investment of time and manpower represented by the IRBs appears to have achieved its desired aim: a reduction in the likelihood of serious abuses of human research subjects.

This goal has been achieved despite profound changes in the national biomedical and behavioral research environment in the years since the human subjects protection program was first implemented. Changes within the past 10-15 years alone include:

- The doubling of expenditures for U.S. health-related research and development

- An increase in non-NIH sponsorship of health research and development to represent at least half the total expenditure

- A 30 percent increase in the volume of NIH human subjects research applications (and a similar increase in the non-NIH sector)

- Extension of human subjects protection to nontraditional research sites, such as community hospitals and clinics involved in cooperative group and community-based research

- Changing patterns of research opportunity reflected most dramatically in the response to the AIDS epidemic, but also found in many other areas, including genetic engineering, human reproduction interventions, and the ongoing development of new drugs and medical devices

- Evolution in societal attitudes toward medical research in which the public no longer avoids the role of research subject out of fear of becoming a "human guinea pig", and instead may even demand the opportunity to enroll in clinical trials

- Widespread discussion (e.g., evening news broadcasts, made-for-TV movies, well-publicized lawsuits) regarding who should bear the costs of therapeutic research, and the effects of a huge industry that supplies health care services for profit

To meet the challenges of a continually evolving biomedical and behavioral research environment without jeopardizing the protection of human subjects in that environment, the IRB system must necessarily be evolving as well. Thus, it is important to examine not only the adequacy of protection provided by the current system, but also the ways in which IRBs have responded to difficult challenges, including the pressure of greatly increased workloads. In addition to present-day challenges, IRB responses are also shaped by the circumstances under which the system was initially created. To understand where the human subjects protection system is going in the future, it is first necessary to take a brief glimpse into its past.

## A. Historical Perspective on Human Subjects Protection Regulations

From 1962 through 1991, the current system for protecting human research subjects was created, piece by piece, largely in response to disclosures of dangerous or controversial biomedical and behavioral research. Such incidents included: the Thalidomide drug tragedy; the 40-year Tuskegee syphilis study; the injection of live cancer cells into elderly patients in the 1960s; and the more recent disclosure of unethical Cold War-era radiation experiments.

Evolving concerns about the use of human subjects in biomedical and behavioral research were met with several key responses. The FDA, in 1962, mandated that investigators must obtain informed consent from subjects. In 1966, the Public Health Service instituted a policy requiring peer committee review of proposals for research that investigators deemed a potential risk to human subjects.

The National Research Act of 1974 (Public Law 94-348) included a requirement for research institutions to establish and operate committees that it termed institutional review boards (IRBs). The Act also transferred oversight of research involving human subjects to a new organization within NIH, the Office for Protection from Research Risks (OPRR), and established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research to guide federal human subjects protection policy. In that same year, human subjects protection regulations governing all research supported or conducted by the Department of Health, Education, and Welfare were issued as 45CFR46, under Section 491 of the Public Health Service Act. With the new regulations, the IRBs -- rather than principal investigators -- became responsible for determining whether potential research subjects are "at risk," and if so, whether the risks outweigh possible benefits to them and the importance of the knowledge to be gained from the research.

The National Commission, which operated from 1975 to 1978, issued a series of influential reports that included the 1978 *Belmont Report*, a seminal analysis of the ethical principles that should govern research with human subjects and the boundaries between research and practice. Based partly on the recommendations of that commission and a subsequent body, the Presidential Commission for the Study of Ethical Problems in Biomedical and Behavioral Research, the Department of Health and Human Services (DHHS) in 1981 issued major revisions of its rules and regulations for the protection of human subjects, and in 1983 provided "additional protections for children involved in research" (Subpart D, 45CFR46). In 1991, the core of the DHHS regulations was adopted by 15 other federal departments and agencies as the Federal Policy for the Protection of Human Subjects (56CFR28004). Supplanting Subpart A of 45CFR46, it became known as the Common Rule.

## B. Human Subjects Protection As Defined By The Regulations

Current federal regulations (45CFR46) mandate various types of protection for participants in biomedical and behavioral research. For example, the regulations decree that physical, psychological, social, or economic risks to human subjects be minimized. Additionally, risks must be reasonable in relation to anticipated benefits, such as providing new knowledge or improving the health of the subject.

To fairly distribute the burdens and benefits associated with research and to guard against systematic injustices, the regulations require the equitable selection of human subjects. This includes taking into account the purposes of the research and the setting in which it will be conducted, as well as the special problems of research involving vulnerable populations, such as children, prisoners, the mentally disabled, and individuals who are economically or educationally disadvantaged. Ideally, socially disadvantaged people, for example, should be no more likely than the socially advantaged to be used as subjects in experiments that offer no prospect of medical benefit or pose greater than normal risks.

The regulations also state that all human subjects must be informed about and clearly understand the proposed research, have the capacity to give consent, and voluntarily decide whether to participate. In addition, the regulations

allow for consideration of the presence or type of incentives (e.g., money, free health care, free contraception, or a variety of other benefits offered to subjects) as possible pressures that limit the voluntary nature of study participation.

The rights and welfare of human subjects are also maintained with regard to issues of privacy and confidentiality. The regulations are designed to ensure that subjects cannot be identified in research results and that confidential information is not improperly divulged.

In response to new concerns and efforts to clarify ambiguities or refine requirements for IRBs and investigators, federal policies, guidelines, and regulations have continually evolved. Three recent instances include language covering "deferred" consent for temporarily incapacitated individuals, human embryo research, and inclusion of women and minorities in clinical research.

## C. Mechanisms for Human Subjects Protection

The regulatory apparatus for overseeing biomedical and behavioral research consists of two principal tiers of review -- local (research institution) and federal. Both tiers are responsible for ensuring that individual researchers and their institutions engaged in projects conducted or funded by any of the departments/agencies that adopted the Common Rule are in compliance with federal laws and regulations governing human subjects protection.

### 1. Local/Research Institution Level

At the research institution level, oversight is done primarily by IRBs responsible for examining research proposals and ongoing studies. In general, IRBs are composed chiefly of scientists at their respective institutions. They are required to have a minimum of five members, at least one of whom is a scientist, one a nonscientist, and one a person not otherwise affiliated with the research institution. To maximize sensitivity to a broad range of social as well as scientific issues, IRBs are also required to consider gender, racial, and ethnic diversity in their membership.

The local nature of most IRBs enables members to be familiar with the research institution's resources and commitments, the investigators' capabilities and reputations, and the prevailing values and ethics of the community and subject population. As a result, IRB judgments on a protocol-by-protocol basis may reflect such factors as institutional values, institutional pressures, and community standards. The individuality and autonomy of local IRBs is further enhanced by terminology in some sections of the regulations that lends itself to variations in interpretation and application.

### 2. Federal Level

At the federal level of review, the NIH Office of Protection from Research Risks (OPRR) negotiates and approves Assurances of Compliance (AOC) -- contract-like agreements that must be entered into by research institutions before engaging in federally-funded human subjects research. An AOC approved by OPRR commits an institution and its personnel to full compliance with federal ethical conduct standards, including informed consent.

In the case of universities and other major research centers that conduct a substantial number of studies and have demonstrated a willingness and the expertise to comply with human subjects protection requirements, OPRR may approve multiple project assurances (MPA) that categorize IRBs, based on the type of research reviewed, as non-medical, non-behavioral, or non-exclusionary (may review both medical and behavioral research). Through an MPA, an institution does not need to reapply for eligibility to receive Department of Health and Human Services funds for each new study approved by its IRB. If violations of human subjects protection requirements occur, OPRR has the authority to impose sanctions in the form of withdrawal of MPAs and, with that action, possible cancellation of research funding.

## D. Major Studies and Reports on Human Subjects Protection

The majority of studies of human subjects protection and related aspects of human subjects research have focused on specific topics, such as risk-benefit assessments, injuries to subjects, consent forms and processes, or particular review committees. Following are descriptions of major studies at both the local/research institution and federal levels that are somewhat more general in nature.

The most comprehensive national evaluation of the institutional review board system was conducted in the late 1970s by the Institute for Survey Research at the University of Michigan, on behalf of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Using multiple methodologies, the Michigan study design provided a detailed picture of the types of research being reviewed by IRBs, the level of effort devoted to IRB review by investigators and board members, and the views of IRB members, institution officials, investigators, and subjects on various topics. These findings fed into the deliberations of the Commission and its report and recommendations on IRBs, many of which were subsequently incorporated into the 1981 revisions of regulations for the protection of human subjects.

Several studies conducted before and after the Michigan survey provided a research-based perspective on the evolution of IRBs. The largest survey prior to 1978 was by Barber et al., who collected data about IRB review activities and outcomes and used hypothetical cases to gather information about espoused standards and self-reported behaviors concerning research ethics. Another important pre-National Commission study was Gray's (1975, 1975) interview and observational study of a particular IRB and of the studies the IRB had reviewed, which provided a link between subjects' experiences and IRB review of specific protocols.

The largest national survey of IRBs conducted since the 1981 revisions of the HHS regulations was a 1983 study by Grundner. Questionnaire data from IRB chairs at 341 institutions was collected, covering topics such as the composition and workload of IRBs, how IRBs were handling the exempt categories defined in the 1981 regulations, and respondents' perceptions about the new regulations.

Another approach to assessing the work and performance of IRBs was explored by the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, when four-member expert teams made one-day exploratory site visits to 12 IRBs in 1983. More recently, Crawford and Bowler in 1989 conducted a preliminary interview and questionnaire study about various aspects of NIH's 12 intramural IRBs. Sieber and Baluyot, in a 1992 national survey of IRBs that handled social and behavioral research, obtained data from 78 chairs or administrators regarding the seriousness of various problems faced by IRBs.

In response to allegations of abuses of human subjects in radiation research conducted or sponsored by the government during the Cold War, the Advisory Committee on Human Radiation Experiments was convened in 1994 and charged with the task of identifying ethical and scientific standards appropriate to evaluate past research, and recommending ways to ensure that wrongdoing could not be repeated in the future. In the course of their deliberations, the Advisory Committee examined both the current federal rules protecting human subjects and the practices of individual biomedical scientists. The final Advisory Committee report, issued in 1995, contained recommendations for improving the current system of protection for human subjects at both the local and federal levels.

Based on a request from the Senate Committee on Governmental Affairs, which had concerns about the adequacy of current oversight of human subjects protection, the General Accounting Office (GAO) explored whether federal oversight procedures reduced the likelihood of abuses of human subjects, and whether weaknesses existed that could limit the effectiveness of the current oversight apparatus. Because of DHHS' annual $5 billion investment through about 16,000 awards involving human subjects and its lead role in setting, monitoring, and enforcing subject protections, GAO focused on DHHS' oversight system, including OPRR. In addition, GAO interviewed federal and research institution officials; reviewed HHS and FDA regulations, procedures, and records;

examined institutional procedures, guidelines, and records; and interviewed scientific researchers, experts in human subjects protection from universities, medical centers, and subjects' rights groups, as well as representatives of the drug industry. This work was carried out in 1994-95, and a final GAO report was published in 1996.

The prior research outlined above provides the groundwork for the current national evaluation. In addition, previous studies offer an intriguing (though inexact) means of assessing whether, as the IRB system continues to evolve in response to the changing face of biomedical research, certain issues nevertheless remain constant.

## E. Purpose

Overall, the presence of local review bodies and federal oversight agencies appears to have heightened the awareness and sensitivity of the research community to the importance of respecting human subjects' rights and welfare. While most of those involved in the human subjects protection system seem to believe it is fundamentally sound, significant changes in the volume, nature, and setting of biomedical and behavioral research have taken place since completion of the comprehensive National Commission study more than 20 years ago and the subsequent revisions in human subjects protection regulations. Based on these considerable alterations in the research landscape, a reexamination of the current program of human subjects protection is called for.

In recognition of that need, the National Institutes of Health (NIH) has contracted for this study of the implementation of the HSP program. The main goal of the study is to greatly improve the systematic knowledge of the universe of active IRBs operating under MPAs. As the group responsible for the largest share of DHHS-sponsored human subjects research, MPA-IRBs also exercise the most local discretion over human subjects protection matters.

## F. Study Design

The study universe was 491 MPA IRBs that were identified as active, defined as performing more than 10 initial reviews per year. As this study pertains to NIH implementaton of the PHS Act, IRBs established under 21CFR50 and 56 and administered solely by the FDA are excluded. The IRBs administered by OPRR cover studies undertaken by PHS and DHHS, as well as those activities funded by other federal agencies that are carried out at institutions holding MPAs with DHHS. Except to the extent that the DHHS IRBs (those administered by OPRR) also review research sponsored by industry or aimed at marketing of regulated products, this study is not attempting to address the undocumented universe of FDA-administered IRBs, for which there is no listing of institutions or IRBs.

The following are key features of the study design:

- The development of the cross-sectional study design and survey instrumentation benefitted greatly from (and would not have been feasible without) the participation of key representatives of NIH, Public Responsibility in Medicine and Research, Applied Research Ethics National Association, and the Council on Governmental Relations.

- Because the purpose of the study was to be able to generalize about the adequacy of IRB review and the burdens of review, random sampling was chosen as the most effective approach.

- Survey administration was successful because more than 2,000 IRB Chairs, Administrators, Institution Officials, Members and Investigators devoted considerable effort to responding to extensive written questionnaires.

- Questionnaires were prepared for each of the five categories of survey respondents:

  -- Chairs and Institution Officials at all IRBs in the study universe received questionnaires

-- 300 IRBs were randomly selected, and Administrators at those IRBs received questionnaires

-- Administrators at the same 300 IRBs were instructed to randomly select four Investigators (who had recently submitted a protocol for initial review) to receive a questionnaire, for a total of 1,200 Investigators

-- 160 IRBs were randomly selected to participate in the Member survey. Administrators at these IRBs randomly selected four current roster Members to receive a questionnaire, for a total of 640 Members.

- Return rates were 80 percent or above for IRB Chairs (n=394), Administrators (n=245), and Institution Officials (n=400); for Members (n=435) and Investigators (n=632), the return rates were 68 percent and 53 percent, respectively.

- The median number of years of IRB service by respondent type was: 8 years (Chairs), 6 years (Administrators), 4 years (Institution Officials), and 4 years (Members); 64 percent of Investigators had 11 or more years of experience conducting human subjects research.

- The electronic database of 2,106 survey responses (some individuals completed more than one questionnaire) contains 9 megabytes of data in 410,000 fields.

It should be noted that the validity of the findings contained herein rests on the truthfulness of the respondents, and on the accuracy of their estimates and factual reports -- two potential limitations of the study design.

## CHAPTER II

## IRB WORKLOAD: ANNUAL VOLUME OF REVIEWS AND CHARACTERISTICS OF INVESTIGATORS AND PROTOCOLS

According to Section 46.102 of the OPRR regulations, research means a "systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge", and a human subject is "a living individual about whom an investigator (whether professional or student) conducting research obtains: 1) data through intervention or interaction with the individual, or 2) identifiable private information." With regard to the oversight of human subjects research, the workload of IRBs is primarily defined by the number of protocols (volume) and characteristics of the research reviewed by IRBs within their particular institutional domains. As well, IRBs are shaped by the types of human subjects protection issues they face -- some of which can be traced to the qualifications and research agendas of the investigators who utilize human subjects.

This chapter profiles human subjects research overseen by study IRBs in terms of: the annual number of reviews responded to (Section A); the characteristics of investigators submitting protocols to IRBs (Section B); and the features of new protocols submitted in 1995, including type of research, source of funding, research methods, and prevalence of multicenter protocols (Section C). The numbers and characteristics of human subjects involved in those protocols, as well as the anticipated risks and benefits of participation, are also described. (Section D). Except for data on number and type of IRB reviews, these findings are based on investigators' reports about specific protocols submitted for IRB review in the most recently completed record year, which usually began in 1995.[3] Differences are noted among subgroups defined by volume, research exclusion code and type of research.[4] [5]

### A. Annual Volume of Reviews

*-- The most critical need is to reduce the workload. Members can't do a thorough, good job when they have a 2-foot stack of documents to read in one week. (High-volume investigator)*

*-- The workload on the chair, IRB members, and myself is heavy and is continuing to grow. (High-volume administrator)*

Since the last national study, the volume of human subjects research has grown steadily, leading some observers to conclude that rising workloads of protocols which must be reviewed and overseen have led to severely over-stressed IRBs (*JAMA,* 1996). In a recent record year, the 491 IRBs in the study universe conducted an estimated 284,000 reviews (within a 95% C.I. of 266,000 to 301,000), including 105,000 initial reviews (exempt, expedited and full board) that accounted for 37 percent of the total; 116,000 continuing/annual reviews (41 percent); and 63,000 reviews of amendments to approved protocols (22 percent). (Figure 1)

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[3]Herein we sometimes use 1995 to indicate the period, but it is always synonymous with the most recently completed record year.

[4]The median annual number of initial (full board and expedited) reviews, 133, was used for volume stratification. IRBs with a lesser or greater number of initial reviews were defined as low- or high-volume, respectively. The cutpoints for the volume deciles were: decile 1=27, decile 2=45, decile 3 = 71, decile 4=100, decile 5 = 133, decile 6 = 173, decile 7 = 250, decile 8 = 350, and decile 9 = 500.

[5]Unless noted, there were no statistically significant differences between high- and low-volume IRBs.

In addition to the above reviews, which consume the majority of total IRB effort, the IRB workload included activities such as responding to reports of within- and out-of-jurisdiction harms to subjects, subjects' complaints and legal actions, and other matters related to individual protocols; carrying out complementary tasks, such as educational sessions for investigators, recruiting and orienting new IRB members, and formulating IRB policies; and the management and administration of the IRB in areas such as recordkeeping, human resources, and new technology. The effort required for non-review activities is discussed in Chapter III, including findings about IRB practices for some activities.

The following looks more closely at the annual volume of initial, continuing/annual, and amendment reviews -- the main portion of the IRB workload. As indicated by these data, the distribution is quite uneven across IRBs. This uneven distribution has strong implications for how IRBs operate (as will become increasingly evident in Chapters III and IV), and may even affect the adequacy of protection (Chapter V).

### 1. Variation Among IRBs

*-- The volume of protocols is low, so review can be comprehensive. (Low-volume chair)*

*-- We review too many protocols at the bi-monthly meetings. (High-volume chair)*

As mentioned above, the yearly volume of 284,000 initial, continuing/annual, and amendment reviews was distributed quite unevenly among IRBs -- perhaps the most distinguishing feature of the IRB landscape. In this regard, the high peaks are the 10 percent of IRBs (in the highest volume decile) with about 105,100 reviews annually, accounting for 37 percent of the national total. (Figure 2) Together, the 246 high-volume IRBs conducted 88 percent of the yearly total [CHC12].[6]

Closer examination reveals that the mix of initial, continuing, and amendment reviews varied moderately, but significantly, across IRBs in different volume deciles (but does not vary predictably according to the amount of volume decrease or increase). For example, the proportion comprising initial reviews varied from 34 percent for IRBs in the highest volume decile to 47 percent for the third (lowest) decile IRB. These differences were offset by greater and lesser proportions of workload attributable to continuing/annual reviews and amendment reviews.

Before turning to additional elements of IRB workload, such as reports of harm outside the context of continuing/annual review, let us look at initial reviews, which consume the largest proportion of IRB effort.

### 2. More About Initial Reviews

The 49 highest volume IRBs accounted for 34,500 initial reviews, 34 times more than the 1,000 reviews conducted in the 49 lowest volume IRBs. Overall, the 105,000 initial reviews conducted annually were split between full-board review (59 percent) and a combination of exempted (15 percent) and expedited reviews (26 percent). These percentages were nearly constant across IRB workload volume deciles. However, the range of variation within each decile was wide. For example, in the highest volume decile, two IRBs expedited more than 80 percent of their initial reviews, while five IRBs expedited 10 percent or less. Overall, 5 percent of IRBs performed only full board initial reviews; 2 percent did no full board reviews; and 95 percent of IRB recorded one or more exemptions and/or expedited reviews. Fifteen percent of all IRBs expedited no initial reviews; 35 percent exempted none.

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[6]Bracketed codes, which will appear throughout the report, refer to questionnaires and specific survey questions; for example, [CHB1] indicates the Chair questionnaire, Section B, question 1. Abbreviations for other survey groups are as follows: IO=Institution Official; AD=Administrator, MB=Member, and IN=Investigator.

The percentage distribution of exempted protocols and expedited initial reviews (i.e., non-full board) by annual volume of initial reviews is shown in Figure 3. The heavy lines on the scattergram partition four equal-sized groups of IRBs: high-volume, high exempt/expedited; high-volume, low exempt/expedited; low volume, high exempt/expedited; and low volume, low exempt/expedited. The median cut point for volume was 133 initial reviews annually, and 33 percent for the proportion of initial reviews that were exempt/ expedited.

### 3. Multicenter Protocols

*-- Many of the most complex and time-consuming protocols we review are for large, multicenter trials. (High-volume member)*

A growing phenomenon in human subjects research is multicenter protocols, such as those for clinical trials that originate elsewhere (i.e., the investigator submitting the protocol to the IRB for initial review is not the overall study director). The regulations allow local IRBs to make their own review determinations on these human studies.

Multicenter protocols represented 30 percent of the total submissions for initial review in 1995.[7] According to chairs, 82 percent of IRBs reviewed one or more multicenter protocols. There was only a slight (but significant) difference in the likelihood of receiving multicenter protocols across IRBs with different workload volumes (87 percent of high-volume IRBs versus 77 percent of low-volume IRBs) [CHC19]. (Figure 4) There was a greater difference by exclusion code: 85 percent of medical and non-exclusionary IRBs reported multicenter protocols, whereas only 38 percent of behavioral IRBs did.

### 4. Harms

Within-Jurisdiction

Chairs reported a total of 2,845 protocols under IRB jurisdiction that were associated with harms to subjects in the recent record year. These were incidences of harms to subjects that IRBs were notified of, other than complaints about inconveniences and minor economic matters such as misscheduled appointments or late payments. Types of harms included: temporary psychological or physical stress or discomfort; minor psychological or medical complications; serious psychological or medical complications; permanent psychological or medical disability; fatal complications; social or legal harm, as could result from a breach of confidentiality with regard to a stigmatizing intervention or condition; or economic harm, such as loss of work time or a patient being responsible for research-associated medical costs that were not covered by the research budget or by third-party payers.

Fifty-six percent of IRBs had zero instances of within-jurisdiction harms [CHC30, CHC31]. Based on the number of within-jurisdiction harms per 100 initial reviews, high-volume IRBs had a slightly lower rate, 9.3 mean protocols per 100 initial reviews versus 14 per 100 for low-volume IRBs.[8] Using the research exclusion categories described in Chapter I, only 12 percent of non-medical IRBs reported harms in jurisdiction, compared to 39 percent of non-behavioral IRBs and 46 percent of non-exclusionary IRBs.

Out-of-Jurisdiction

[7] In 30 percent of the cases (particularly for high-volume (IRBs), these numbers were estimated.

[8] Mean calculated for those IRBS that have within-jurisdiction harms; i.e., zero-harm IRBs excluded.

The Food and Drug Administration (FDA) requires that all unanticipated harms (i.e., kinds of harms that were not expected or harms that were more serious than expected) be reported by investigators to the sponsor who, in turn, must notify all other investigators. Frequently, these are Adverse Drug Reports (ADRs). Investigators who are notified of such reports of unanticipated harm must send a copy of the notice to their local IRB.

According to chairs, IRBs received a total of 64,600 reports of "out-of-jurisdiction" harms in the most recently completed record year [CHC27]. The maximum was 5,000 such reports for one very high-volume IRB (tenth decile). The median rate of reports of out-of-jurisdiction harms per 100 initial reviews varied according to workload volume, with an almost three times greater rate for high-volume IRBs compared to their low-volume counterparts (80 and 28 harms per 100 initial reviews, respectively). (Figure 5) As a group, non-medical IRBs reported zero out-of-jurisdiction harms.

## B. Investigators

The number of individual investigators conducting human subjects research under the auspices of the study IRBs ranged between 35,000 and 45,000 in 1995.[9] The mean number of years of hands-on experience for these investigators was 12.1.[10] Seventy-two percent of investigators reported they had first conducted research with human subjects prior to 1990, and 33 percent said they had first done so prior to 1980 [INA3]. Seventeen percent had one year or less experience. (Figure 6) At the time they submitted their designated protocol (the one they reported on in the Investigator Questionnaire), 67 percent of respondents were full-time faculty [INA2]. The remainder featured a diverse mixture of research staff (7 percent), graduate or health professions student (6 percent), attending physicians (5 percent), clinical staff (4 percent), and other, e.g., adjunct clinical faculty or part-time faculty (11 percent).

When asked how many human subjects protocols they had submitted for initial review in the past three years, the mean was 8.6 for all investigators. Seventeen percent
indicated more than 10 protocols, while 14 percent of investigators said one protocol only [INA4].[11]

More than half of the investigators (55 percent) identified the broad field(s) in which their education was concentrated as clinical sciences (including medicine, nursing, and other), with nearly equal percentages specifying behavioral sciences, biomedical sciences, social sciences (24, 21, and 20 percent, respectively) [INA1]. The percentage of investigators with an education concentrated in clinical biomedical sciences was greater for high-volume IRBs (73 percent) compared to low-volume IRBs (57 percent). Similarly, 44 percent of investigators at low-volume IRBs reported behavioral sciences and social sciences education, compared to 27 percent of high-volume IRB investigators. As expected, 85 percent of investigators at non-behavioral IRBs reported clinical/biomedical education, and investigators with epidemiology education tended to be at non-behavioral IRBs. Over 88 percent of those at non-medical IRBs indicated behavioral/social sciences education.

## C. Protocol Characteristics

[9] Rough estimate derived from investigators' responses (question INA4) about the number of human subjects research protocols.

[10] In 19 percent of cases, these dates were estimates.

[11] In 33 percent of cases, the numbers were estimates.

### 1. Kind of Research

Among the protocols that came before their IRB, 63 percent of chairs reported that the most prevalent kind of research involving human subjects was clinical research involving data collection on matters of physical or mental health through direct clinical intervention or interaction with patients or healthy volunteers (e.g., phlebotomy, radiation, drugs, surgery, or non-invasive testing, examination or manipulation). Behavioral sciences research was a distant second (19 percent), followed by biomedical sciences research not involving direct intervention by a clinician (e..g, research using existing specimens or samples) (7 percent), and educational research and social sciences research (at 6 percent and 3 percent, respectively) [CHC15]. The likelihood of clinical or biomedical research being identified as the most common kind of research was somewhat greater for high-volume as compared to low-volume IRBs (72 percent vs. 54 percent, respectively). (Figure 7) At non-behavioral IRBs, 92 percent of the research was identified as clinical and biomedical. Conversely, the odds of conducting a combination of behavioral sciences, social sciences or educational research were somewhat greater for low-volume IRBs (24 vs. 13 percent), and much greater at non-medical IRBs, at 85 percent vs. 24 percent at other IRBs.

Investigators were also asked to describe the kinds of research conducted under the protocol designated in their questionnaires as follows: clinical research (51 percent), behavioral research (14 percent), and biomedical research (9 percent) emerged as the most frequently mentioned types, with the remainder (26 percent) spread across educational research, social sciences research and other kinds [INB17]. Investigators at high-volume IRBs reported clinical/biomedical research at a rate of 69 percent, compared to 55 percent at low-volume IRBs.[12] At non-behavioral IRBs, the figure was 70 percent.

### 2. Research Methods

IRBs must be able to identify and consider the human subjects protection issues associated with an array of methods used to conduct the various types of research involving human subjects. With regard to the types of methods used in their respective projects, investigators' reports are shown in Figure 8, which presents the use of 16 methods for clinical/biomedical and behavioral/social research protocols [INB18]. For example, random subject selection was more prevalent (26 percent) in behavior/social research than in clinical/biomedical (11 percent). In general, the differences between the two types of research were expected: clinical/biomedical was more likely to involve double-blind design, placebo administration and invasive procedures, while behavioral/social was apt to involve interviews and self-administered questionnaires, in addition to random selection of subjects.

Methods also varied according to research exclusions. For example, placebo administration was never reported by investigators at non-medical IRBs; interviews predominated at those IRBs. Almost all invasive testing or exams occurred at non-behavioral and non-exclusionary IRBs, and almost never at non-medical IRBs. In addition, 60 percent of investigators noted that personal identifiers had been collected, with no differences by IRB volume decile, research exclusion code, or protocol research type [INB19].

### 3. Funding Sources

*-- Drug companies are threatening our investigators to have IRBs approve protocols or else risk having the research dollars moved somewhere else. (High-volume institution official)*

[12] Clinical/biomedical research includes clinical research, biomedical science, and epidemiology. Behavioral/Social research includes social science, behavioral science, educational research, and health services research.

*-- There is too much concern about how research is funded. Whether a study is funded by departmental funds, NIH funds, or funds from a commercial enterprise is irrelevant to the protection of human subjects. (Low-volume investigator)*

According to chairs, NIH (25 percent) and industry (25 percent) were the leading sources of funding for protocols reviewed by their IRB, together accounting for about one-half of protocols that were implemented [CHC40]. (Figure 9) Institution funds (11 percent) and pre-existing resources (17 percent), which are both internal sources, and a combination of other external sources (besides NIH and industry), including federal, philanthropic and state funds, together supported the remainder of funded protocols (22 percent). Protocols reviewed by IRBs with no exclusions and non-behavioral IRBs were twice as likely to draw on institutional funds (26 and 32 percent, respectively) when compared to non-medical IRBs (13 percent). As such, at non-medical IRBs, 33 percent of protocols were implemented with existing funds resources; at non-behavioral IRBs, only 15 percent were. Conversely, at non-behavioral IRBs, 33 percent of protocols were implemented through industry funding, compared to only a few percent at non-medical IRBs.

In addition, among the 63 percent of investigators who applied externally for sponsorship of their protocol, applications to non-NIH funding sources outnumbered applications to NIH by almost 2 to 1, with no difference by IRB volume [INB14-15]. Thirty-four percent of investigators at non-medical IRBs applied for NIH funding; only 23 percent of investigators at non-behavioral IRBs did.

## D. Subject Involvement

Section 46.111 of the regulations specifies equitable selection of human subjects, taking into account the purposes of the research, the setting, and the special problems of research involving vulnerable populations and involved persons (e.g., children, prisoners, pregnant women). Additional language pertains to the equitable inclusion of women and minorities.

### 1. Number

Investigators reported a median of 50 subjects had been involved in their studies; the average of 836 was boosted by the numerical effect of some very large population studies overseen by IRBs[13],[14] [INB20]. Despite a range that extended to 80,000 subjects, only five percent of investigators said 1,000 or more subjects had been involved; at the other end of the spectrum, 21 percent of protocols had 10 subjects or less. With regard to high- and low-volume IRBs, the median number of subjects involved was 45 and 70, respectively; thus, low volume IRBs typically reviewed protocols having larger numbers of subjects. For clinical/biomedical research protocols, the median number of subjects reported was 30; for behavioral/social, the median was 123. Similarly, non-medical IRBs averaged more subjects per protocol than either non-exclusionary or non-behavioral IRBs.

### 2. Eligibility

Investigators were asked to identify the demographic characteristics of individuals eligible for participation in their designated studies [INB21]. With few exceptions, protocols were open to subjects regardless of race, ethnicity or gender. In contrast, the reproductive status of women, age, student status, and presence of vulnerabilities such as mental illness were likely to limit eligibility for study participation and to show differences by type of research. For

[13]Total subjects reported by investigators sampled was nearly one-half million.

[14]Forty-one percent of respondents indicated the numbers provided were estimates.

example, pregnant and nursing women were less likely to be eligible for clinical/biomedical types of research or protocols under non-behavioral IRBs. (Figure 10)

### 3. Duration of Participation

Investigators were asked to provide, in the one time-unit that was most appropriate, the amount of time, on average, that had elapsed from a subject's enrollment in a particular study to the end of his or her participation [INB22]. As with number of subjects, there was no typical protocol in terms of duration of subject participation.

For those who said the duration of participation was consistent enough to determine an average duration per subject and who responded to the question, their answers were as follows: one hour (12 percent); up to 8 hours (16 percent); 9-50 hours (5 percent); 1-3 weeks (12 percent); 1-6 months (33 percent); and 1 or more years, up to 25 (22 percent).[15]

### 4. Anticipated Risk/Benefit

*-- The greatest strength of the IRB is it makes investigators consider the risks/benefits of their research. (High-volume investigator)*

*-- IRBs are too oriented toward risk and often estimate risk as much greater than it is. They tend to undervalue the benefits from procedures that involve even a low level of risk. (Low-volume investigator)*

Risks

According to the regulations, risks to subjects must be minimized (e.g., through the use of sound research design) and reasonable in relation to anticipated benefits and/or the importance of the knowledge that may reasonably be expected to result (Section 46.111).

Investigators were asked to identify the types of risks to subjects they anticipated when they submitted their protocols for initial review, and to evaluate the predicted level and likelihood of those risks [INB7]. The high-volume IRBs were somewhat more likely to have protocols with anticipated medical risks; all other types of risks were similar between high- and low-volume IRBs. Of those investigators who reported medical or psychological risk, 24 percent reported both types of risk.

Types of risk were highly correlated with type of research (clinical/biomedical or social/behavioral). (Figure 11a) For instance, 64 percent of investigators with clinical/biomedical protocols reported medical risk, while only 7 percent of those with behavioral/social protocols did so [INB17]. Psychological risk was reported by 40 percent of investigators with behavioral/social protocols, 26 percent with clinical/biomedical protocols, and 35 percent for all other types of research protocols.

A similar pattern of differences existed across types of IRBs. For example, medical risk was anticipated by 77 percent of non-behavioral IRB investigators, 3 percent of non-medical, and 44 percent of non-exclusionary. Psychological risk was reported by only 18 percent of non-behavioral IRB investigators, and by 42 percent of non-medical IRB and 30 percent of non-exclusionary IRB investigators . Social risk was reported by 3 percent of non-behavioral IRB investigators and by 10 percent of all others.

[15] In 18 percent of cases, these figures were estimates. Also, 56 percent of investigators said duration was not consistent enough to determine average duration.

In terms of level and likelihood of risk, a three-quarters or greater majority of protocols with a medical, psychological, or social risk had a low level of risk and less than 10 percent likelihood of occurring. The exceptions were protocols with psychological risk that had a 10 percent or greater likelihood of that type of risk occurring.

Further, when asked if they anticipated different risks of harm from study participation for subjects in the control group versus subjects in the experimental group, half of investigators responded no, and over one-third said the question was not applicable; thus, only a modest percentage (less than 15 percent) expected such differential risk levels [INB8]. Fourteen percent of investigators with clinical/biomedical research protocols reported having different risks for the control group, while only 6 percent all other investigators did so.

Benefits

Investigators were also asked to identify the types, level, and likelihood of benefits to subjects that were anticipated when their protocols were submitted [INB6]. Analysis revealed the majority of investigators expected for each type of benefit both a medium or high level of beneficial effect and a 50 percent or greater chance of the benefit occurring. Investigator expectations of benefits to subjects also varied significantly, depending on type of research. For example, 75 percent of investigators with clinical/biomedical protocols expected medical benefits, compared to 14 percent with behavioral/social protocols. (Figure 11b) (Expectations of psychological benefits did not differ significantly by type of research.) Psychological benefits were expected by investigators for between 41 and 49 percent of protocols, depending on type of research. Educational benefits were expected for 60 percent of behavioral/social protocols, but only 38 percent of clinical/biomedical research. Social benefits were expected for 32 percent of social/behavioral research and16 percent of clinical/biomedical.

### 5. Patient Condition and Health Care

Nearly half (46 percent) of investigators indicated that some subjects (experimental or control) were seeking or receiving clinical care for the mental or physical condition under study [INB23]. These investigators were then asked to indicate the health conditions of subjects who were seeking or receiving clinical care [INB24]. At non-medical IRBs, only 15 percent (of subjects) were seeking or receiving care. For clinical/biomedical research, 58 percent of subjects were seeking/receiving care, while in the case of behavioral/social research, only 12 percent were [INB17].

Almost one-half of those investigators (47 percent) said their subjects had very serious conditions; within that group, one in three protocols (or 16 percent of all protocols) had subjects with either a terminal condition, medical emergency, or attenuated ability to comprehend. Subjects with non-serious or moderately serious conditions participated in 25 percent and 31 percent of protocols, respectively. In protocols at high-volume IRBs, subjects had more (and more serious) health conditions than in protocols conducted at low-volume IRBs.

Regarding protocols in which subjects were hospitalized and/or received medical care solely for the purpose of the research (15 percent of the total) [INB25], investigators were also asked to indicate who paid for subjects' health care [INB26]. The costs were paid by the research sponsor in 51 percent of protocols with hospitalization and/or medical care; a third party payor (30 percent); the subject (13 percent); the institution or department (15 percent); and "other," such as health care system, "don't know," or gift funds (14 percent). Some investigators (11 percent, with the majority at high-volume IRBs) indicated more than one payor reimbursed these costs.

### 6. Potentially Difficult Subjects Protection Issues

Chairs were substantially more likely to report their IRB had encountered potentially difficult issues in one or more protocols with regard to consent, as compared to risk/benefit or genetics (the other categories they were asked about) [CHC18]. Issues relative to assent procedures for children and for cognitively impaired subjects arose in 88 percent and 80 percent of protocols, respectively. The other difficult consent issue reported on by chairs -- research

in acute and emergency care settings -- was encountered by 57 percent of IRBs. Protocols with the issue of continued access to experimental intervention after completion of the research were encountered by 59 percent of IRBs. Issues of genetics research and gene therapy were encountered by 50 and 24 percent of IRBs, respectively.

As a subgroup, high-volume IRBs were much more likely to report one or more protocols embodying one or more of these potentially difficult issues; however, the incidence rate (occurrences per 100 protocols submitted for initial review) and distribution by type of difficult issue were very similar to those of low-volume IRBs. Thus, high-volume IRBs encountered more protocols with difficult issues because they reviewed more protocols -- not because the protocols they reviewed were more likely to entail difficult issues.

## CHAPTER III
## IRB PERSONNEL AND POLICY/PRACTICES

Institutional Review Boards rely on the direct participation of thousands of people to carry out human subjects protection. This requirement is strongest for high-volume IRBs, which have adapted to their larger workloads both by adding personnel and making adjustments in practices. Thus, the number of members and administrative staff, frequency of full board meetings, and duration of meetings were all greater for high-volume IRBs than for their low-volume counterparts. This chapter describes the characteristics of the five groups of people most directly involved in IRB operations -- chairs, members, administrators, administrative staff, and institution officials (Section A), and examines the policies and practices implemented by IRBs in response to 45CFR46 (Section B). Differences are noted among subgroups of IRBs defined by volume, research exclusion code, or rate of use of exempt/expedited allowances.[16]

### A. Personnel

*-- The greatest strength of the IRB is the superb people with a variety of backgrounds and extensive experience. The people are the key. (High-volume investigator)*

*-- It was only my pleasure to work with these highly educated, professional, supportive people. (Low-volume investigator)*

*-- This IRB needs a major overhaul. (High-volume investigator)*

The regulations specify a minimum of five IRB members with varying cultural and racial/ethnic backgrounds who are sufficiently knowledgeable to promote complete and adequate review of research activities commonly conducted by the institution. Members must be drawn from qualified persons of both genders, and more than one profession is to be represented (Section 46.107).

Reference is made in the regulations to a designated member who acts as IRB chairperson (Section 46.110). According to OPRR records, about 94 percent of IRBs also have an administrator who assists the chair and members. With the exception of IRBs with the smallest workloads, the workforce typically includes administrative support staff under the direction of the IRB administrators. Additional key personnel involved in making IRBs work are the institution officials responsible for monitoring the DHHS/NIH institutional assurances.

In a recently completed record year, 8,414 individuals -- chairs, members, administrators, administrative staff, institution officials -- were directly involved in running the 491 IRBs in the study universe (Figure 12). An overview of their demographic characteristics is shown in Figure 13. IRB personnel are predominantly white and well-educated, with chairs and members more likely to be male, and administrators more likely to be female. Based on self-descriptions provided in the surveys, the various participants in IRB oversight and operations can be characterized as follows.

#### 1. Chairs

*-- The IRB's greatest strength is the fantastic commitment and skill of the chair. (High-volume institution official)*

[16]Unless noted, there were no statistically significant differences between high- and low-volume IRBs.

*-- The current chair is a godsend. (Low-volume institution official)*

*-- There is little respect by the chair for members of the committee holding Ph.Ds. (High-volume member)*

The chairs of IRBs in the present study brought considerable experience to the position.[17] [CHA1]. They had a mean of 5.2 years serving as chairs of the study IRBs and a range of total IRB experience of less than 1 year to more than 32 years, Regarding total experience on any IRB, as chair or member, the mean for chairs at high-volume IRBs was 10.4 years, compared to 8.8 years of service for low-volume chairs [CHA2]. In addition, 62 percent of chairs reported being full-time faculty with the organization for which their specific IRB was performing reviews. Examples of other positions held by chairs include attending physician, administrator, research or medical staff, and part-time faculty [CHA3]**.**

With respect to other characteristics, chairs were predominantly white (95 percent) and male (77 percent) [CHA6 and CHA8]. Chairs' areas of education were largely concentrated in the broad field(s) of clinical sciences (51 percent) and biomedical sciences (39 percent) [CHA5], and the vast majority (93 percent) listed a doctoral degree as their highest level of educational attainment [CHA4]. Behavioral (22 percent) and social sciences (15 percent) accounted for the largest remaining percentages. Educational backgrounds in epidemiology, statistics, law, ethics, and humanities were also represented at IRBs in all workload volume deciles.

**2. Members**

*-- The membership is quite diverse, yet members communicate well with each other and show great respect for the opinions of all participants. (Low-volume institution official)*

*-- IRB members have an excellent understanding of the research areas they review. (Low-volume investigator)*

*-- The IRB needs more persons who are actively involved in research themselves. The experience of many members is dated. (Low-volume investigator)*

According to OPRR records updated in the summer of 1995, the 491 study IRBs had 6,923 members, with membership ranging in size from 5 (the minimum mandated by law) to 44 members. The mean number of members for IRBs in the lowest volume decile was 10.5, compared to a mean of 19.7 members in the highest volume decile. (Figure 14) As IRB workload increased, the number of members rose, with roughly one additional member gained for every two volume deciles.

With regard to total IRB experience, members as a group had contributed about 38,000 years of service on any IRB. They had served on their specific IRBs for a mean of 4.7 years [MBA1]; total IRB service (including IRBs at other institutions) was a mean of 5.5 years [MBA2]. The vast majority (86 percent) indicated they were affiliated with the institution(s) for which their particular IRB performed reviews [MBA3]. When asked to describe the professional capacity in which they served the institution, 56 percent of members affiliated with the institution said they were full-time faculty, with clinical staff and research staff comprising 11 percent and 7 percent, respectively [MBA4]. Six percent of members had administrative positions.

In terms of other characteristics, members were predominantly white (92 percent), and more than half (58 percent) were male [MBA8 and 10]. Members' educations were in the broad field(s) of clinical sciences (42 percent),

[17]There were fewer individual chairs (478) than study IRBs (491), because 13 individuals chaired two IRBs.

biomedical sciences (19 percent), behavioral sciences (17 percent), and social sciences (20 percent) [MBA6]. Overall, the majority of members (72 percent) possessed a doctoral degree. High-volume IRBs were substantially more likely to have non-scientist members (affiliated and non-affiliated) who had training in either law or ethics (11 percent).

OPRR regulations specify that each IRB must have at least one member whose primary concerns are in scientific areas, one member whose primary concerns are in nonscientific areas, and one member who is not otherwise affiliated with the university (Section 46.107). Seventy percent of members were affiliated scientists; the remainder were about equally divided between affiliated non-scientists (13 percent), such as persons educated in law and business, and non-affiliated members (14 percent). Most of the non-affiliated members were also non-scientists (10 percent of total members).

The vast majority of members agreed with the statements, "My duties as a member of this IRB are clearly defined" (76 percent), and "I am satisfied with what I have been able to accomplish as a member of this IRB" (74 percent). Conversely, only 5 percent of members were in strong or moderate agreement with the statement, "I would prefer not to have to serve on this IRB" [MBC7].

### 3. Administrators

Administrators indicated they had staffed, in any capacity, the specific IRB or any other IRB for a mean of 7.2 years, with 29 years being the maximum reported [ADA1]. In terms of the total number of IRBs overseen by an administrator, the vast majority (84 percent) were responsible for a single IRB, and 15 percent had 2 to 6 IRBs [ADA8]. With regard to demographic characteristics, administrators were generally white (89 percent) and female (85 percent) [ADA4 and ADA3], and the highest educational degree achieved was commonly a Bachelor's degree (28 percent), followed by a high school diploma (19 percent) or a Master's degree (18 percent) [ADA2].

### 4. Administrative Staff

*-- The greatest strength of the IRB is the superb staffing by (overworked) staff. (High-volume institution official)*

*-- The staff has such outstanding skill, yet it is not well utilized because of guidelines. (High-volume member)*

According to OPRR regulations, provisions should be made for sufficient staff to support the IRB's review and recordkeeping duties (Section 46.103). Administrators reported that 498,000 person-hours were expended in a recent year on IRB activities by administrative support staff working under the supervision of the IRB administrator (see Chapter IV below). Although a count of individual staff members was not requested in the survey, this number of person-hours suggests a workforce of at least 250-300 full-time equivalent staff persons -- and undoubtedly many more individuals, because administrative support is a part-time duty at many IRBs. Administrative staff distribution is very uneven across IRB volume deciles: 15 percent and 100 percent of the lowest and highest decile IRBs have administrative staff, respectively. Given the rising prominence of administrative staff in the IRB workforce (particularly at high-volume IRBs), more attention should be given to the characteristics of administrative staff members in the future.

### 5. Institution Officials

The regulations state that the assurance shall be executed by an individual authorized to act for the institution and to assume on behalf of the institution the obligations imposed by the human subjects protection policy (Section 46.103). Based on survey results, institution officials had assumed responsibility for the DHHS human subjects protection assurance a mean of 6.1 years ago, with a range of less than one to 34 years. Twenty-one percent of

institution officials had served in that capacity for 10-plus years, while 12 percent had been in the position for less than 1 year [IOA1]. As with administrators, some institution officials oversee multiple IRBs (22 percent), an arrangement that is more likely to be found at high-volume IRBs (28 percent).

Institution officials indicated the authority to which IRBs directly report is most commonly identified as the provost or vice president for research (35 percent). Other oversight authorities included: hospital administrator or provost/vice president in the academic sector (9 percent); Boards (of Trustees or Directors) (4 percent); commissioners and agency administrators (2 percent); and presidents (2 percent), executive vice-chancellors, or a combination of titles (6 percent) [IOB2].

## B. Policies and Practices

The regulations allow considerable discretion in the practices used to fulfill protocol review and other IRB operating responsibilities. Although certain mandates exist (e.g., the composition of the IRB membership (Section 46.107), what defines a quorum for an IRB meeting (Section 46.108), the recording and retention of meeting minutes (Section 46.115)), the practices used to carry out IRB responsibilities are mostly locally defined. These practices include: the use of expedited or exempt categories, scheduling of IRB meetings, and the use of primary/secondary reviewers to prepare for full board review. Such local discretion leads inevitably to variation in how similar matters are handled. For example, in designing this study, large differences were found across IRBs in terms of how they organized their records.

The following presents a portrait of IRB practices that generally follows the life cycle of human subjects protection for an individual protocol. The first subsection describes enabling IRB activities, such as educational presentations and distribution of model consent forms, designed to facilitate investigator submission of appropriately protective human research protocols. The steps taken by IRBs to prepare protocols for review at formal IRB meetings are presented in the second subsection, and the final subsection discusses IRB practices that occur during and after formal IRB meetings.

### 1. Enabling Policies and Activities

#### a. Provisions for Exempt and Expedited Review

*-- IRB performance could be improved if definitional clarity regarding what types of research should be either exempt or subject to expedited IRB review were established. (Low-volume member)*

*-- Expedited/exempt reviews should be handled initially by another paid staff. (High-volume member)*

*-- General classes of non-invasive protocols should be given blanket non-board approval. (Low-volume investigator)*

*-- All research involving human subjects should undergo IRB review. Reduction of burden on the IRB should not be the issue. (Low-volume member)*

In recognition of the fact that some human subjects research involves negligible or very minimal risk to the rights and welfare of subjects, the 1981 regulations designated six categories of research (found primarily in the educational, social, and behavioral sciences) as exempt from review, and 10 categories as suitable for expedited review. These allowances for exemption from review and expedited review are not mandatory; each IRB retains local discretion about how to respond to the exempt and expeditable categories.

Exempt Research

*-- The IRB should be more willing to exempt studies that meet the criteria described in the DHHS "Exempt Categories of Research." (Low-volume member)*

*-- We spend too much time on projects that are exempt, and some that should be exempt are processed by expedited review. (High-volume member)*

Section 46.101 enumerates the six categories of research activities deemed suitable for exemption from the policy governing research with human subjects. According to chairs, about one-half or fewer protocols eligible for exemption were actually exempted from review, depending on research category [CHC21, CHC22]. (Figure 15) The next most common practice relative to exempt research was expedited review. For example, about 45 percent of IRBs required some form of expedited review for the exempt category, "existing data and specimens without identifiers" (one of the categories of exempt research most likely to be reviewed as exempt).

Seventy-three percent of administrators indicated the IRB was routinely involved in determining or confirming whether protocols were exempt from human subjects protection review [ADB13]. Sixty-seven percent of administrators involved in exempt determination/
confirmation stated the IRB routinely made the determination for investigators developing human subjects protocols, while the remaining 33 percent said the IRB routinely confirmed investigators' determinations [ADB14].

Expedited Research

*-- We need to identify research protocols that meet the requirements for expedited review and reduce the workload. (High-volume member)*

*-- I think the time [spent on] review is wasting many people's time. An expedited review could be used for most educational studies. (Low-volume investigator)*

Section 46.110 of the regulations pertains to expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research. Under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB. Disapproval of research activity can occur only under non-expedited procedures.

For both high- and low-volume IRBs, expeditable research involving drugs and devices not requiring investigational exemptions was least likely to receive expedited review, at 23 percent and 28 percent, respectively. (Figure 16) In contrast, 85 percent of high-volume IRB chairs reported that research involving nail and hair clippings received expedited review, compared to 65 percent of low-volume IRB chairs. Research that included excreta was also highly likely to receive expedited review and to register a similar difference between high- and low-volume IRB chairs (80 percent and 57 percent, respectively), as was research concerning dental plaque (76 percent and 55 percent, respectively).

In sum, for every exempt and expeditable research category, chairs indicated there were substantial proportions of IRBs -- ranging between 25 and 77 percent, depending on IRB volume and research category -- that choose as standard practice some form of review that was more rigorous than specified by the regulations.

### b. Educating Investigators, Members, and Staff

*-- Full IRB participation is very time-intensive. The problem is time for self-education, not just protocol review. (High-volume member)*

*-- My orientation to my role and responsibilities was poor -- I was given a copy of IRB guidelines to read. (Low-volume member)*

*-- An institution-sponsored (perhaps mandated) investigator training program would make the IRB function better, because initial submissions would be better, requiring fewer revisions prior to approval. (High-volume chair)*

Educational Sessions

Seventy-two percent of chairs reported that educational sessions had taken place in the most recently completed record year, with high-volume IRB chairs nearly twice as likely as their low-volume counterparts to do so. With regard to the specific educational goals of learning about the requirements for human subjects protection, learning about the informed consent process, and learning about procedures associated with IRB review, chairs identified investigators and/or students and chairs and/or members as the chief target audiences. (Figure 17) According to chairs,18 percent of IRBs (three-quarters of whom were high-volume) focused on all indicated educational goals, as well as all audiences [CHC3].

Orientation of Members

In terms of new member orientation, 77 percent of members said they had first learned about what was expected of them as an IRB member in an oral briefing by the IRB chair, staff, or member(s). Other methods for learning about their duties included the specific IRB's handbook or guidelines (62 percent), federal regulations for the protection of human subjects (52 percent), and other written information on IRBs and research with human subjects (49 percent) [MBB1].

Guidance Materials

*-- The recent development of a human subjects manual is a big help in ensuring that investigators address important issues. (Low-volume investigator)*

A near unanimous majority of chairs (96 percent) reported the IRB or the institution had provided investigators with human subjects protection guidelines that explained matters such as when to obtain IRB approval, what to do in preparation, and/or the steps necessary to initiate review [CHC1]. With regard to routinely provided local documents (i.e., the investigator received the item without specifically requesting it), model consent form(s) or consent form checklists and protocol content checklists were substantially more likely to be identified than other local and federal guidance materials [CHC2]. (Figure 18)

### c. Conflict of Interest

According to institution officials, in cases where the institution determines that an investigator has a significant financial interest in his or her research and that research requires IRB approval, the institution's typical policy is to notify the IRB only if management of the potential conflict of interest requires such notification (51 percent); routinely notify the IRB of the investigator's financial interest and of the steps that will be taken to manage the potential conflict (31 percent); or "other" (17 percent) [IOA3].

### d. Written Materials Required for IRB Submission for Initial Review

With regard to written materials submitted for initial review, administrators reported that all (or nearly all) IRBs required consent forms, IRB review request forms, a summary protocol description and/or a full copy of the protocol [ADB6]. In addition, 91 percent of administrators specified "other" types of materials required for submission, such as recruitment ads, research instruments, and letters of agreement to participate by other departments or individuals. Administrators from high-volume IRBs were significantly more likely to report that the following materials were required: full copy of the study protocol; investigator brochures; summaries of animal studies; departmental approval findings from other institutional review groups; and "other" materials (e.g., letters of collaboration or cooperation from other sites, IND/IDE, etc.).

#### e. Written Materials Required for Continuing/Annual Review

The regulations require IRBs to conduct continuing review of approved research not less than once a year (Section 46.109). According to administrators, the written materials most likely to be required for continuing/annual reviews were: reports of harms to subjects (96 percent); description of any changes in the protocol since it was approved (93 percent); completed forms requesting IRB review (87 percent); and current consent form(s) (84 percent) [ADB7].

### 2. Preparing for Review

#### a. Checking Submitted Materials for Completeness

When protocols and accompanying materials were first received from investigators, the practice in 98 percent of IRBs was to check them for completeness. If an investigator had omitted information necessary for review, she/he was usually asked to immediately supply the missing item(s) so review could proceed on schedule. In IRBs that checked for completeness, the IRB administrator or another member of the IRB administrative staff was most likely to perform this function (79 percent). In 31 percent of IRBs, the chairs checked the completeness of submissions for full board review [CHC23a].

#### b. Assigning Primary or Secondary Reviewers

Full Board Initial Review

Eighty percent of IRBs have adopted the practice of using primary and secondary reviewers, who then bring their assessment to the full board meeting for the larger group to consider during initial review. At three-quarters of high-volume IRBs, administrators or other IRB support staff assigned primary/secondary reviewers for full board initial review; at the majority of low-volume IRBs, the IRB chair performed that task [CHC23b]. (Figure 19)

Full Board Continuing/Annual Review

The IRBs were evenly split on whether primary reviewers are routinely assigned for full board continuing/annual review, with high-volume IRBs somewhat more likely to adopt this practice [CHC25]. Of those IRBs that assigned primary reviewers to such reviews, 30 percent reported the chair was typically assigned responsibility; 26 percent said the responsibility fell to one or more members assigned on some other basis; 24 percent noted the responsibility went to the IRB member who performed the primary review at the time of initial review; and about 18 percent said it was assigned to one or more IRB members who were predesignated as being responsible for primary review of continuing/annual review reports.[18] [CHC26]

[18] A small group of 7 respondents to question CHC26 selected more than one response choice.

### c. Distribution of Materials

According to administrators, IRB members typically received protocols and related materials a mean of 7.5 days prior to board meetings, with a range extending from 2 to 30 days before the meeting [ADB11].[19]

Expedited Initial Review

Administrators indicated that prior to expedited initial review, chairs and the designated reviewer(s) were the persons most likely to receive the submitted materials. These were generally completed forms requesting IRB review, summary descriptions of protocols, and consent forms [ADB8].

Full Board Initial Review

Administrators noted that prior to board meetings for protocols undergoing full-board initial review, specific types of materials were routinely distributed (either in hardcopy or electronically) [ADB9]. These included a full copy of the study protocol (investigator written) that was distributed to: the designated primary reviewer (or primary review subcommittee) (55 percent); the chair (51 percent); the full board (58 percent); and others, usually the IRB administrator (10 percent). With regard to consent form(s), they were distributed to: the designated primary reviewer (or primary review subcommittee) (52 percent); the chair (62 percent); the full board (94 percent); and others (11 percent).

Overall, high-volume IRBs distributed more types of materials to more types of participants, especially to primary reviewers. Materials not applicable to local procedures or types of review comprised 18 percent of all responses for low-volume IRBs, as compared to 9 percent for their high-volume counterparts.

Full Board Continuing/Annual Review

For the majority of materials distributed prior to meetings for protocols undergoing full-board continuing/annual review, the full board (all IRB members) was the group most likely to receive such materials, including completed forms requesting IRB review, a summary description of the current study protocol, a description of any changes in the protocol since it was approved, and a summary description of subject enrollment [ADB10]. Chairs and the designated primary reviewer (or primary review subcommittee) were the persons next most likely to receive these materials. Similar to full board initial reviews, high-volume IRBs distributed more types of materials to more types of participants, particularly to primary reviewers.

### d. Member Involvement in Expedited Review and Primary Review

In the previous six months, 42 percent of members indicated they had conducted expedited reviews [MBB6], and 64 percent said they had conducted primary review of protocols slated for full board review in that time period [MBB8].

### e. Member Preparation for Full-Board Initial Review

Thirty-seven percent of members described their typical practice with regard to examining protocols in preparation for full-board initial review as becoming generally familiar with the content of most protocols, while another 36 percent said it was to review most protocols in depth to identify issues that required clarification and/or discussion

[19] In 35 percent of cases, these figures were estimates.

by the IRB [MBB9]. Another 13 percent scanned protocols, 9 percent referred to them during meetings, and 5 percent used some other review practice.

#### f. Expedited Continuing/Annual Reviews

At 60 percent of IRBs, the chair typically performed expedited continuing/annual reviews. Most of the remaining IRBs turned the task over to a predesignated member or group of members such as a continuing review committee (13 percent), to members assigned on some other basis (13 percent), or to the member who performed the expedited initial review (8 percent) [CHC24].

#### g. Identifying Questions/Issues for Full Board Attention

According to chairs, the person(s) who identified questions/issues for full board attention was: the chair (70 percent); the IRB administrator or other IRB staff (52 percent); the full board (30 percent); another IRB member (27 percent); executive committee or subcommittee of the IRB (8 percent); or other, including consultants, the vice chair, etc. (4 percent) [CHC23c].

#### h. Obtaining Additional Protocol Information

Chairs indicated that the person(s) who obtained additional information about the protocol from the investigator in preparation for full board review was: the IRB administrator or other IRB staff (74 percent); the chair (60 percent); another IRB member (31 percent); the full board (16 percent); or other, including the primary reviewer (2 percent) [CHC23d].

### 3. During and After IRB Meetings

#### a. Number of Meetings and Total Meeting Time

*-- At present, the IRB meets once a year. A bi-annual schedule would perhaps expedite the review process. (Low-volume institution official)*

*-- We need to meet more than twice a month. The meetings are too long. (High-volume institution official)*

Except in the case of expedited review, the regulations require review of proposed research to take place at convened meetings at which a majority of IRB members are present, including at least one member whose primary concerns are in nonscientific areas (Section 46.108). Based on chairs' reports for 1995, a total of 4,834 full board meetings were held by IRBs in the study, with a range for individual IRBs extending from 1 to 50 IRB meetings [CHC7]. The mean annual total of full board meeting time ranged from 8.6 hours for the lowest volume deciles to 50.2 hours for the highest volume IRBs. (Figure 20) The typical full board meeting lasted about 1 hour, 45 minutes for low-volume IRBs, compared to 2 hours, 25 minutes for high-volume IRBs [CHC8].[20] The longest and shortest meetings were 7.5 and 0.5 hours, respectively. When compared to low-volume IRBs, high-volume IRBs met more frequently and for longer periods of time; the aggregate meeting time during a recent year for all high-volume IRBs (8,900 hours) was twice as long as the total meeting time for all low-volume IRBs (4,150 hours).

#### b. Board Meeting Time by Topic

[20]According to 4 percent of chairs, there was no typical meeting length. In 35 percent of cases, the figures on meeting time were estimates.

*-- Initial review is very thorough. We have a broad cross-section of expertise, and people take their jobs seriously. (Low-volume member)*

*-- For some reason, staff responsibilities have been reduced, and more is required of the board for annual updates. (High-volume member)*

For the typical full board meeting, chairs indicated that about 66 percent of the meeting time was devoted to protocols submitted for initial review and 13 percent of meeting time was spent on continuing/annual review. In addition, 7 percent was devoted to amendments, 6 percent to reports of harm to subjects, and 7 percent to other activities such as planning, training, discussing issues in IRB management, etc. [CHC11]. (Figure 21)

Nearly all members (97 percent) indicated that topics relative to whether a study's design and procedures minimize the medical, psychological, legal, educational, social, or economic risks to subjects or whether subjects require additional safeguards to protect their rights or welfare were subjects of discussion during IRB deliberations. Additional topics that were likely to arise included the circumstances under which consent by a subject's representative was adequate for participation in research (82 percent of members), and whether a proposed activity constituted human subjects research (67 percent) [MBB10]. Of the eight topics listed, the average number covered was greater for high-volume IRBs (7 topics) than for low-volume IRBs (5 topics).

### c. Administrator Involvement in Review

In the most recently completed record year, 61 percent of administrators had substantively reviewed new protocols, amendments to ongoing studies, and/or protocols submitted for continuing/annual review [ADB3].

### d. Investigator Availability During Meetings

*-- The IRB should have the principal investigator attend the meeting to explain methods and rationale. (High-volume investigator)*

Low-volume IRBs were somewhat more open than high-volume IRBs to investigator presence at their meetings [ADB12]. Regarding availability of investigators to IRBs while discussions of protocols were taking place, 42 percent of administrators from low-volume IRBs, compared to 17 percent from high-volume IRBs, noted that investigators were routinely encouraged to attend the meetings or to be reachable by telephone. In contrast, 41 percent of administrators from high-volume IRBs, compared to 22 percent from low-volume IRBs, reported that investigators attended the meetings, or were on call, only when requested by the IRB.

### e. Use of Consultants

*-- The IRB should develop a process for expert consultation on projects for which the IRB lacks expertise (High-volume investigator)*

According to the regulations, an IRB may, at its discretion, invite individuals with competence in special areas to assist in the review of issues that require expertise beyond (or in addition to) that available on the IRB. However, such individuals are not allowed to vote with the IRB (Section 46.107). With a potentially broad spectrum of types of protocols to review, IRBs may have compelling reasons to enlist the support of experts with special competence. About half of chairs (46 percent) reported their IRBs used one or more consultants in the most recent record year, with most uses of consultants (four out of five cases) entailing review of a specific protocol. At high-volume IRBs, consultants were used a median of 33 times per 100 initial reviews (with one such IRB using consultants 350 times), compared to a median of 1.4 times per 100 initial reviews for low-volume IRBs [CHC4, CHC5, CHC6].

### f. Notifications

Certifying Office

Section 46.109 of the regulations states that the IRB must notify investigators and the institution in writing of its decision to approve or disapprove a proposed research activity. In the matter of how an institution's certifying offices learn whether a protocol has IRB approval, 47 percent of institution officials indicated the IRB periodically notified Grants and Contracts, or another certifying office, of all approvals, while 46 percent said the IRB notified the investigator of approval, and the investigator notified the certifying office. In addition, 25 percent said the IRB notifies the certifying office upon request of the investigator, and 14 percent reported the certifying office electronically accessed information maintained by the IRB. Twenty-six percent specified "other" in responding to this question [IOA2].

Review Disposition

According to administrators, in addition to the submitting investigators (who were always notified), the Sponsored Research Office or Grants and Contracts Office was the next most likely to be notified about the disposition of an initial review, continuing/annual review, review of an amendment, or review of a within-jurisdiction harm. Depending on the type of review, the above office was notified by as many as 50 percent of IRBs (initial review dispositions) or as few as 26 percent (disposition of harms under IRB jurisdiction). In addition, depending on type of disposition, 6 to 20 percent of IRBs notified "others", such as the Vice-Provost for Research, the Dean of the Office of Research Services, and/or the protocol coordinator [ADB19].

Protocol Initiation

When asked how the IRB routinely learned that an approved protocol was initiated, 72 percent of respondents reported the IRB sent the investigator a notice at the time of continuing/annual review and requested information about initiation versus non-initiation of the protocol; 22 percent said the Sponsored Research or Grants and Contracts Office notified the IRB when funding of the protocol was awarded; and 22 percent stated the investigator notified the IRB when the protocol was initiated. Seventeen percent specified "other" ways of learning that an approved protocol was initiated [ADB20]. Of those administrators who specified "other," the majority said the IRB routinely learned that an approved protocol was initiated at the time of the continuing/annual review, while others stated the IRB heard about initiation from various offices, including the Medical Center's R&D Office, the Office of Research Administration, or the Office of Research, or that it is not routinely notified.

Harms to Subjects

When asked to identify who, during the most recently completed record year, was routinely notified of reports of harms to subjects (when those reports were made to the IRB outside of the context of continuing/annual review), 74 percent of administrators indicated the IRB chair and/or the IRB administrator were routinely notified. In addition, 46 percent stated the full board was routinely notified; 13 percent said the primary reviewer(s) of the initial protocol (including, if applicable, secondary reviewers and members of the primary review subcommittee) routinely received notification; and 16 percent specified "others", including the adverse event subcommittee, the institution official, and the full board [ADB21].[21]

For the most recent year, 37 percent of respondents identified the chair as the person who decided whether and what action should be taken on harms to subjects under the jurisdiction of the IRB, while 32 percent said it was the full

[21]Included in the base for calculating these figures are the 26 percent of administrators who indicated their IRB was not notified of any harms in 1995.

board who performed this function [CHC33]. Others making such decisions were: an IRB administrator or other IRB staff (16 percent); one or more other IRB members (14 percent); an institution official (13 percent); and "other," including an investigator, or OPRR (3 percent).

According to chairs, in 68 percent of cases where out-of-jurisdiction harm reports were received by the IRB, the IRB administrator or other IRB staff always reviewed the report. In addition, such reports were always brought to the attention of the full board nearly half of the cases [CHC28].

### C. Views of Greatest Strengths of IRBs

Eighty-nine percent of chairs described one or more attributes of their specific IRBs, with the majority of comments (57 percent) highlighting the characteristics of individuals who comprise the board, and another 26 percent focusing on attributes of the board as a working group. The remainder of comments about IRB strengths (18 percent) pertained to the positive characteristics of IRB staff and others who supported IRB efforts, such as consultants and institution officials. Responses were very similar among high- and low-volume IRBs, with the exception that high-volume chairs were more likely to comment on the strengths of administrative staff -- perhaps due to the fact that low-volume IRBs were less likely to have assigned, or be as dependent upon, administrative staff [CHB13].

While the 97 percent of institution officials who responded to the same question provided answers that were quite similar to those of chairs, investigators were more likely to praise the IRB in terms of the board as a working unit first, and the positive characteristics of individual board members second. Like chairs and institution officials, investigators also described the characteristics of IRB staff and others who support IRB efforts as an important strength [IOB10, INC3].

## CHAPTER IV
## REASONABLE BURDEN, SUFFICIENT EFFORT

The regulations that govern human subjects protection in federally-funded biomedical and behavioral research are widely considered among the most demanding in terms of the amount of effort it takes to comply with them. There are two fundamentally divergent viewpoints on effort. One focuses on reasonableness: too much effort might signal inefficiencies in the protection process that could place an unnecessary burden on institutions and investigators in fulfilling their commitments to human subjects. The other focuses on sufficiency: too little effort might signal a breakdown in the system that could undermine the adequacy of protection for subjects.

Based on factual and opinion data gathered for the study, Chapter IV describes the person-time expended on IRBs, and then explores the sufficiency and reasonableness of that effort by examining inter-IRB variations in effort and opinions data. Are human subjects protection requirements too much of a burden (as many argue), or do they allow institutions to expend too little effort (as others claim)?

For a recent record year (1995), Section A presents findings on the amount of person-time (effort) devoted to IRB reviews and other human subjects protection activities for each of the five classes of IRB personnel. Section B reports an analysis of person-time per review, including a discussion of IRB review-related effort by investigators. Section C offers other information relative to effort, such as the use of IRB meeting time and duration of initial review, and Section D presents opinions about the effort devoted to human subjects protection.[22]

### A. Person-Time Effort Devoted to IRB Activities

*-- The IRB is a particularly burdensome university committee due to the amount of reading and the meeting schedule. (Low-volume institution official)*

*-- The major problem with any busy, properly functioning IRB is the time required of the members and administrators to do their job. The time commitment is substantial. (High-volume member)*

Long missing from the discussion of human subjects protection are nationally representative data on the amount of effort expended on IRB activities by various IRB personnel at the research institution level -- chairs, members, administrators, administrative staff, and institution officials.[23] This section describes the amount of effort by IRB personnel collectively, as well as the distribution of effort among personnel categories and IRB activities. These data, which pertain generally to 1995, set the stage for a closer examination of the amount and mix of labor expended per IRB review. A discussion of the amount of time spent by investigators on initial review is also included.

#### 1. Total Effort: All IRB Personnel

[22]Unless noted, there were no statistically significant differences between high- and low-volume IRBs.

[23]Narrowly construed, as is the case herein, total IRB effort equals the sum of the labor expended in a year on the human subjects protection activities of IRBs by these five types of personnel. A broader definition adds other costs associated with human subjects protection that are not easily assigned to IRBs; for example, the investigator labor and other costs associated with IRB review and implementing human subjects protection procedures, such as obtaining informed consent and tracking and storing consent forms. Even more subtle components of total cost include any opportunity costs, such as slowed research.

In a recent record year, approximately 1.67 million person-hours were devoted to running the 491 IRBs in the study universe (95% C.I.). A breakdown of the total annual person-time reveals that, in roughly equal proportions, members (516,000 person-hours), administrative staff (498,000 person-hours), and administrators (472,000 person-hours) together accounted for 89 percent of total effort. In addition, chairs supplied 7 percent of the effort (122,000 person-hours), while institution officials contributed 4 percent (62,000 person-hours). (Figure 22)

Because the amount of effort expended yearly by an IRB varies according to annual workload, the results indicated that all categories of personnel expended more labor as the volume of reviews increased. Additionally, the relative proportion of total IRB effort provided by IRB chairs, members, administrators, administrative staff, and institution officials varied significantly between the lowest and highest volume IRBs (excluding the IRB administrator), with the largest differences found in the number of hours provided by IRB administrative staff. (Figure 23) As workload increased, the percentage of total effort supplied by IRB administrative staff almost quadrupled, rising from 13 percent for IRBs in the lowest volume decile to 47 percent for IRBs in the highest volume decile.

### 2. Chair Effort

The total of 122,000 person-hours devoted annually by chairs to IRB activities was distributed unevenly among IRBs; for chairs in the lowest and highest workload volume deciles, the mean number of annual person-hours was 72 and 386, respectively [CHA11].[24] There was a strong positive correlation between workload size (indicated by annual volume of initial reviews) and the number of hours of chair effort per year; chairs of IRBs in the highest volume deciles devoted a mean of 378 hours per year, compared to 61 hours for chairs of the lowest volume IRBs.

Despite the variation in amount of time devoted by chairs, there was no difference between the highest and lowest volume IRBs in the percentage of their time applied to specific activities. During the most recently completed record year, chairs participated in a total of about 80,000 IRB initial reviews, or 75 percent of total initial reviews; thus, the majority of chairs' time (54 percent) was spent on matters specific to the initial review of protocols. (Figure 24)

Secondarily, chairs' time went to a combination of continuing/annual reviews and reviews of proposed amendments to ongoing studies and reports of harms to subjects (21 percent); to educating themselves and/or others on issues of human subjects protection and/or developing local IRB policies and procedures (13 percent); and to managing and administering the IRB (12 percent) [CHA11a]. For chairs, there were only slight differences in the distribution of time usage across these activities due to IRB volume of initial reviews, with variations of only a few percentage points across activity categories.

### 3. Member Effort

The estimated total of 516,000 member person-hours devoted annually to IRB duties was also unevenly distributed among the 6,923 IRB members of the study IRBs. Collectively, the members of IRBs in the highest volume decile reported a mean of 2,128 hours per year, compared to a mean of 294 hours for members of the lowest volume IRBs [MBB4].[25] On average, individual members at the highest and lowest volume IRBs spent 108 and 28 hours per year, respectively. (Figure 25)

Part of the difference in mean member-hours across workload volume deciles is explained by differences in the number of IRB members, which, as noted in Chapter III, ranged from a mean of 10 to 19 per IRB for the lowest and highest volume IRBs, respectively.

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[24] In 52 percent of the cases, these figures were estimates.

[25] In 62 percent of cases, these figures were estimates.

Members were also asked how many initial reviews they had participated in during the past six months.[26] Members of IRBs in the highest volume decile reported a mean of 54 such reviews per member, while the mean for the members of lowest volume IRBs was 7 reviews [MBB5]. The mean percentage of total annual initial reviews that members actively participated in ranged from a high of 88 percent in the lowest decile of IRB activity to 16 percent in the highest volume decile. Thus, at the highest volume IRBs, which have significantly more members per IRB and more frequent meetings, each individual member participated in a relatively small proportion of total initial reviews.

Forty-three percent of members had conducted one or more expedited reviews in the previous six months [MBB6]; in that same time period, 64 percent had conducted primary reviews of protocols slated for full board review [MBB8]. Overall, 28 percent of members had conducted both expedited and primary reviews, with those in high-volume IRBs somewhat more likely to have performed both types.

### 4. Administrator Effort

The 472,000 person-hours that administrators devoted to activities on behalf of the IRB in the most recently completed record year were skewed to the higher volume IRBs. For the highest volume IRBs, the mean number of administrator-hours per month was 122, compared to a mean of 12 hours per month for the lowest volume IRBs [ADB2].

On average, administrators spent 31 percent of their IRB hours dealing with matters specific to the initial review of protocols [ADB2a], and an almost equal share of their time (30 percent) managing and administering the IRB. In addition, they devoted 19 percent of their time to dealing with matters specific to continuing/annual review, amendments to ongoing studies, and reports of harms to subjects, and 12 percent was absorbed by education on issues of human subjects protection and/or developing local IRB policies and procedures. Administrators reported devoting 7 percent of their hours to "other" activities, such as adverse drug reports, training staff, and reviewing protocol modifications requested by the IRB. (Figure 26)

### 5. Administrative Staff Effort

Based on administrators' reports, IRB administrative staff devoted an estimated 498,000 person-hours annually to the work of the IRBs, with a much higher concentration of effort at high-volume IRBs [ADB5]. The percentage of IRBs that had any administrative staff rose from 40 percent of IRBs in the lowest decile to 85 percent of IRBs in the highest decile. (Figure 27) At the IRBs in the highest volume decile, administrative staff support totaled just under 110,000 person-hours (or an average per IRB of about 2,245 hours per year engaged in IRB work), while the lowest volume IRBs had a total of 2,490 hours per year of administrative staff effort and an average per IRB of 51. Forty-one percent of administrators indicated they were the only administrative staff person on hand.

### 6. Institution Official Effort

An estimated 62,000 person-hours of institution officials' time was expended on duties directly related to the role of official of record responsible for the institution's human subjects protection assurance. The range extended from 12 to 2,100 hours per institution official [IOB3]. Additional statistics in this regard included a mean of 127 hours per year (for both high- and low-volume IRBs), with no significant differences by volume decile.

### 7. Investigator Effort on Initial Review

[26]For 56 percent of respondents these numbers were estimates, and 12 percent of members reported they did not know the answer to the question.

Although they are not core IRB personnel, investigators conducting human subjects research are heavily involved in initial review. When asked to indicate how many hours were spent preparing a specific protocol for initial IRB review and responding to any IRB questions/requests for modifications in the content of initial review, almost two-thirds of investigators reported they had spent 8 or fewer hours on that initial review, with a median of 5 hours [INB3].[27] (Figure 28) Five percent of investigators spent 40-plus hours on initial review; however, most of those were conducting full board clinical or biomedical protocols in which subjects were seeking (or already receiving) medical care.

The mean person-hours spent by investigators preparing for and completing IRB full board initial review was twice as much as the average amount of investigator effort spent per expedited review, 13.9 hours vs. 7.4 hours, respectively.

If the time spent by investigators solely in IRB initial review was included, the number of hours of total effort devoted to IRB activities would increase by over 50 percent; investigators spent about 840,000 person-hours in 1995 on IRB initial review-related activities. Although not as labor intensive on a per-protocol basis, the investigators also spent time on other forms of IRB review (e.g., continuing/annual review) that could substantially increase their total effort. A full accounting of the burden of human subjects protection should also include the time it takes research staff to conduct the consent process and other human subjects protection measures taken as individual protocols are implemented, thus adding considerably to the millions of person-hours already identified.

## B. Effort Per Review

The amount of per-protocol effort devoted to IRB review is indicative of the burden, as well as the due diligence, of review. Combining the data on IRB workload and person-time utilization, the average amount of effort per review was calculated and examined.[28] The analysis revealed that irrespective of type of review -- initial, continuing/annual, or amendments -- the pattern of differences between high- and low-volume IRBs was consistent. Typically, the IRBs in the lowest volume decile spent about two times more person-time per review than IRBs with the highest workloads. (Figure 29)

The leading candidate explanation for this difference in effort per review is the extent to which high- and low-volume IRBs vary in their use of personnel, especially members and administrative staff, and review process streamlining measures (e.g., extensive use of allowable expedited and exempt research categories). The findings above, for example, indicate extensive reliance on administrative staff effort at high-volume IRBs compared to their low-volume counterparts. Presumably, administrative staff perform checks for completeness and other review-related activities that decrease the effort required for substantive review by IRB chairs, members and, in most cases, administrators; through economies of scale, the total effort needed per review is reduced. The following examines in

[27] In 54 percent of cases, the figures were estimates.

[28] This required the allocation of chair, member, administrator, administrative staff and institution official time to various IRB activities, including initial, annual/continuing and amendment reviews. Chairs and administrators provided the most complete and detailed information about the amount and use of their IRB time. For IRB members, administrative staff and institution officials -- the other core IRB personnel -- the person-time data are less detailed in terms of the percentage of time devoted to specific IRB activities. Since members and administrative staff relate to chairs and administrators, respectively, the time distributions for the latter were estimated using distributional factors from the former. In other words, the distribution of time among IRB activities for members and administrative staff was based on the averages for chairs and administrators in the same decile. Stepping back to consideration of the full amount of labor devoted to IRB review activities, systematic assumptions were made about how IRB person-time was spread among various types of review (using meeting time and other distribution factors), and then total effort per review was calculated.

greater depth the estimated effort per review, focusing on the amount per type of review and the mix of labor involved.

### 1. Effort Per Initial Review

*-- The committee would function more efficiently if protocols could be reviewed by professionals prior to submission to committee, so obvious errors would already have been dealt with. (Low-volume chair)*

The average effort of all personnel per initial review was 7.1 hours for IRBs in the highest volume decile and 14.9 hours for the lowest volume IRBs. Moreover, the proportions of person-time devoted to initial review by chairs, members, administrators, administrative staff and institutional officials shifted rather dramatically as IRB workload increased. For the lowest volume IRBs, it is estimated that 81 percent of the initial review effort came from a combination of chairs (11 percent), administrators (23 percent) and members (47 percent). For an initial review conducted by the highest volume IRBs, chairs, administrators, and members together accounted for a substantially smaller (49 percent) share of the effort, while the share of effort from administrative staff increased from 7 percent for the lowest volume IRBs to 49 percent for the highest volume. (Figure 30)

Looking more carefully at the IRB subgroups defined by the interaction of volume and rate of exempt/expedited (see Chapter II, p. 10) reveals even greater differences in mean total hours (all personnel) per initial review (Figure 31). Low-volume IRBs with a less than average rate of exempt/expedited reviews spend three times more effort per initial review (16.1 hours) than high-volume IRBs with a higher than average rate of exempt/expedited reviews (4.9 hours).

### 2. Annual/Continuing Review

*-- The required process for annual review needs to be overhauled; most IRBs do not have enough staff or willing board members to re-review approved projects annually in a comprehensive way. (High-volume institution official)*

*-- The current practice of requiring full committee reviews of renewals seems an unsupportable commitment of scarce IRB resources. (High-volume institution official)*

The effort expended per continuing/annual review was substantially lower than the effort per initial review -- about one-seventh as much; the highest and lowest volume IRBs spent 1.3 hours and 2.8 hours, respectively. In general, administrators, and administrative staff accounted for a somewhat larger proportion of the effort on annual/continuing reviews, offsetting a decreased proportion of effort from IRB members. This was true even for IRBs with the lowest workloads. Nonetheless, the general phenomenon of greatly heightened involvement by administrative staff in reviews carried out by IRBs with high workload volumes held for annual/continuing review, with administrative staff accounting for 40 percent of effort at the highest volume IRBs, compared to 16 percent at the lowest volume IRBs.

## C. Other Information on Effort

*-- This IRB is very efficient and handles a large number of studies (average of 40 per month) in less than two hours. (Low-volume member)*

*-- Discussion is often too long. Many members enjoy hearing themselves talk. (High-volume member)*

### 1. Meeting Time Per Review

The average number of minutes of IRB meeting time per initial review is a previously used indicator (GAO, 1996) that signals the amount of full board consideration given to a protocol, but ignores the substantially greater amounts of effort spent on review activities preceding the actual meeting, i.e., time spent by chairs, administrators and administrative staff on pre-review activities, and by members, chairs and administrators on primary and secondary reviews.

Based on data provided by IRB chairs, the mean number of meeting minutes per full board and expedited initial review was 21.3 and 3.9, respectively, for IRBs in the low volume decile [CHC7-12]. (Figure 32) Thus, the average meeting time per full-board initial review at the lowest volume decile IRB was seven times longer than for IRBs in the highest volume decile. Similar variation across volume deciles was indicated for expedited initial reviews (and continuing/annual reviews, and amendment reviews). To put this difference in perspective, consider that the meeting time per full-board initial review at the highest volume IRBs was somewhat less than the meeting time per expedited initial review at IRBs in the lowest volume decile.

The effect on meeting time per full-board initial review of assigning primary/ secondary reviewers was negligible for high-volume IRBs; however, for low-volume IRBs, the amount of effort was reduced by one-half, from 18.3 minutes for protocols without, to 9 minutes for protocols with, primary/secondary reviewers.

### 2. Duration of Initial Review

Regarding the number of calendar days that had elapsed from the day the protocol was first submitted through the day that notification of the final disposition (approval or disapproval) of initial IRB review was received, 41 percent of investigators indicated 30 days or more, and 13 percent said 60 days or more.[29] Overall, the median was 28 days (mean of 41 days) for completion of initial review, and the median duration for expedited initial review (25 days) was about one-half the median duration for full board initial review (48 days) [INB4]. Closer examination revealed the effect of type of initial review -- full board or expedited -- on duration; 66 percent of expedited initial reviews were completed in 8 to 30 days, compared to 44 percent of full-board reviews. (Figure 33)

### 3. Unimplemented Protocols

The reports of investigators, based on what happened to specific protocols, indicated the rate of protocol implementation was 84 percent [INB13]. Nonetheless, the majority of chairs reported that fewer than three-quarters of the protocols reviewed by their IRBs were eventually implemented [CHC39]. The difference between chairs' and investigators' reports of protocol implementation might be explained by differences in perspective. Investigators reported on a single protocol about which they were intimately familiar, while chairs were asked to estimate a general protocol implementation rate -- a statistic that many IRBs do not calculate.

According to investigators, the vast majority (84 percent) of human subjects research protocols approved by IRBs were eventually carried out, and only about 16 percent of IRB-approved protocols were never implemented (see above, Protocol Implementation). This finding contradicts the notion that a high proportion of effort expended on initial review is wasted on protocols that are never conducted.[30]

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[29] In 52 percent of cases, the figures were estimates.

[30] Previous conjecture about the rate of unimplemented protocols was perhaps overly influenced by an NIH application success rate that is rather low. As it turned out, NIH research applications were a smaller-than-expected fraction of the total IRB workload -- about one-quarter. In other words, although NIH funding success rates are low, the number of human research protocols competing for NIH funding was small relative to the total number of IRB-reviewed protocols.

### 4. Multiple IRB Reviews

Twenty-three percent of protocols were reviewed by more than one IRB (regardless of expedited or full board type), and seven percent underwent review by three or more IRBs [INB5]. Investigators spent a mean of 11 hours preparing an initial review protocol for single-IRB review, compared to 16 hours for review by more than one IRB. Only 6 percent of behavioral/social protocols were reviewed by more than one IRB.

### 5. Effect of Inclusion Policy

The majority of investigators (58 percent) reported they had not experienced effects as a result of the 1994 federal mandate to include women and minority-group members in human subjects research sponsored by NIH [INC7]. However, 23 percent said the mandate had increased their awareness of the potential value to research and society of including a diverse subject population, while equal percentages (12 percent) indicated the mandate caused them to prolong the recruitment of subjects for one or more studies, or had increased the cost of research for one or more studies.

## D. Opinions About Burden

When asked their opinions about burden for a specific IRB, the responses of chairs, members and investigators to several questions indicated, in general, they considered the burden to be a reasonable one, even compared to other federal regulations governing health research, such as animal care and use and biosafety.

### 1. Overall Efficiency

*-- Our IRB runs with exemplary efficiency. (High-volume chair)*

*-- I would like to see a great improvement in the efficiency of the board and their staff in turnover of paperwork. (High-volume investigator)*

*-- The IRB's greatest strength is that it's responsive to researchers' needs for quick turnaround. (High-volume investigator)*

Equally high percentages of chairs and members (87 percent and 83 percent, respectively) agreed with the statement that "This IRB runs with reasonable efficiency." Although a majority of investigators (64 percent) also agreed with the statement, they were less likely than chairs and members to do so [CHB12, MBC6, INC2]. (Figure 34)

The investigators who chose not to agree with the statement on efficiency were evenly split between a neutral response on the five-point scale (18 percent) and disagreement (16 percent). Only a very small 3 percent strongly disagreed.

### 2. Getting into Inappropriate Areas

Although relatively small percentages of chairs and members (7 and 13 percent, respectively) agreed with the statement, "This IRB gets into areas that are not appropriate to its function", investigators were more than twice as likely as chairs to answer in the affirmative (18 percent) [CHB12, MBC6, INC2].

# CHAPTER V
# ADEQUACY OF PROTECTION

This chapter presents findings on the adequacy of human subjects protection relative to the 491 MPA IRBs in the study universe[31]. These findings are based on opinion data/ratings and factual reports provided by more than 2,000 individuals who are intimately involved in carrying out institution-level human subjects protection -- albeit from somewhat different perspectives. Section A presents respondents' general opinions and ratings of adequacy, while Sections B, C, and D contain, respectively, respondents' reports on Concerns, Modifications, and Other Outcomes of Review; Other IRB Actions; and Reports of Potential Problems.

## A. General Opinions and Ratings Relative to Adequacy

As everyday participants in the human subjects protection process, IRB chairpersons, members, administrators, institution officials, and investigators conducting human subjects research are uniquely well-informed about the adequacy of the human subjects protection system. Their survey responses addressed various topics related to adequacy, including opinions of overall adequacy, investigators' views on the effect of initial review on their protocol, and ratings of the relative impact on human subjects protection of IRB activities and other influences like general investigator awareness. Additionally, the responses of core participants contain several, more subtle indicators of adequacy, such as opinions on the effects of IRB review on scientific quality, bias or lack of expertise on the part of IRB members, and chairs' reports on serious investigator non-compliance, including participation in unapproved research.

In responding to multiple opinion questions on the subject of adequacy, a strong majority of respondents indicated that IRBs generally provide sufficient human subjects protection. However, investigators typically registered somewhat less positive opinions on protection adequacy than those more closely involved with IRBs, such as members, staff or overseeing officials. Nevertheless, the consistency of responses to the same questions across multiple respondents groups and for IRBs with different-sized workloads attests to the high level of agreement among all types of respondents that the protection afforded human subjects is generally adequate in research conducted at their institutions.

### 1. Rating of Overall Adequacy

*-- The IRB is very effective at overseeing research to protect the rights and welfare of patients. (High-volume investigator)*

*-- At times it appears that the IRB is trying to protect the institution rather than the patient. (High-volume investigator)*

*-- The greatest strength of the IRB is its commitment to the protection of human subjects. (Low-volume chair)*

Chairs and members were nearly unanimous in agreeing with the statement that "This IRBs protects the rights and welfare of human subjects" [CHB12, MBC6]. With regard to investigators, 83 percent agreed with that statement, including 55 percent who were in strong agreement [INC2]. (Figure 35)

[31] Unless noted, there were no statistically significant differences between high- and low-volume IRBs.

### 2. Effect of Initial Review on Protocols

*-- There is more emphasis on protecting subjects than on making things easy for researchers. (High-volume member)*

*-- This committee gets too bogged down in critiquing details of each study that go far beyond the protection of human subjects. (Low-volume member)*

*-- The review was careful and thorough. (Low-volume investigator)*

When investigators were asked, "In your opinion, what overall effect on human subjects protection did initial review of this protocol by this IRB have?", 39 percent reported that initial review had either considerably or somewhat strengthened the human subjects protection aspect of their protocol. Further analysis revealed that the 43 percent of investigators who had modified their protocols based on issues raised by the IRB during initial review [INB9] (see below p. 47) were about 1-1/2 times more likely to express the opinion that human subjects protection had been either somewhat or considerably strengthened than were investigators who had not made IRB-prompted modifications [INB11]. (Figure 36)

### 3. Effect of IRB Action vs. Other Influences at the Institution

When asked to rate various influences on the adequacy of human subjects protection at their institution in terms of estimated impact, a substantially greater percentage of chairs than investigators rated the impact of IRB actions as high, at 82 percent to 58 percent, respectively. (Figure 37) However, with regard to the impact of general investigator awareness brought about by the existence and implementation of human subjects protection regulations, investigators rated it somewhat higher than did chairs (63 percent and 51 percent, respectively). Chairs' and investigators' ratings of the influence of actions taken by investigators during development of their protocols and of general investigator awareness of liability for harms to subjects were similar or exactly the same. For both groups, the influence on human subjects protection of instruction of investigators was ranked the lowest overall [CHB11, INC5].

IRB members and institution officials were also asked to rate the impact of the above influences [MBC5, IOA4]. Members' ratings were largely in agreement with those of chairs, except in the case of general investigator awareness resulting from human subjects protection guidelines, where 55 percent of members (as compared to 67 percent of chairs) rated the impact as high. Across the five influences, the percentage of institution officials who rated impact as high was 8-14 points greater than chairs' ratings of the same influences.

### 4. Relative Effect of Different IRB Activities

In assessing the effect of various IRB-performed activities on promoting human subjects protection, nearly two-thirds of investigators rated the impact of initial review as high. For the other five types of IRB activities designed to ensure protection (e.g., review of routine reports of progress, review of reports of harms, and education of investigators regarding human subjects protection), the percentages of investigators who rated the impact as high clustered in the 25 to 36 percent range [INC1].[32] (Figure 38)

### 5. Effect on Scientific Quality

*-- There is relatively minimal attention to the scientific detail. (High-volume investigator)*

[32]The percentages of respondents who indicated their experience was too limited to form an opinion are not included in the following responses to question INC1.

*-- The IRB at this institution spends too much time reviewing protocols for scientific merit before review of the consent form can be considered. This is not our job. (Low-volume member)*

*-- I would like to see more effort put into scientific discussion, and less into the language of the consent form. (High-volume member)*

Scientifically flawed human studies make unacceptable any risk to human subjects' rights and welfare. While nearly equal majorities of chairs and members (56 and 55 percent, respectively) agreed with the statement that the scientific quality of research done on human subjects is improved by IRB review, a substantially smaller 37 percent of investigators were in similar agreement [CHB12, MBC6, INC2]. (Figure 39)

**6. Influence of Workload on Protection Adequacy**

When IRB members were asked their views on the possible effects on review of the IRB workload, 93 percent termed it either heavy, but falling within a range that could be managed without compromising the quality of review (47 percent), or appropriate (i.e., the workload was neither too heavy nor too limited) (46 percent) [MBC1]. Thus, only a modest 4 percent of members believed that review quality was possibly compromised by heavy workload. An additional 3 percent said the workload was too limited or below a critical mass needed to develop expertise in review of human subjects research.

**7. Bias/Lack of Expertise**

*-- There is an interpretation of legal and ethical issues that yields disturbing ways of framing issues. This is not particular to this IRB, but is part of the larger system. (High-volume member)*

*-- There is too much medical influence and investigator bias, and not enough focus on ethics and the protection of human subjects. (High-volume member)*

*-- The greatest strength of the IRB is an excellent understanding of the research areas they review. (Low-volume investigator)*

*-- Our board was reviewing studies for which our backgrounds were somewhat limited. (Low-volume chair)*

Because bias and/or lack of expertise can seriously undermine adequacy of protection, IRB members must be able to understand the human subjects aspects of scientific protocols to achieve an adequate level of subjects protection. Twenty-one percent of investigators, as compared to only 8 percent of chairs and 11 percent of members, agreed with the statement that IRBs have difficulty handling some types of research properly because of bias and/or lack of expertise [INC2, CHB12, MBC6].

**8. Member's Ability to Participate in Review Discussions**

Members were asked about their level of participation in IRB review discussions over the previous six months. On eight topics that commonly arose during IRB review, such as whether a study design minimized risks or whether to require continuing review more frequently than once a year, a small proportion of members (between 5 percent and 15 percent) reported deferring to other IRB members more knowledgeable about the topic [MBB10].

**9. Relative Impact/Burden of Federal Requirements**

*-- Something is wrong with the equation when the Federal government regulations, as interpreted by our IRB, require work that in the long run proves to be lost effort and wasted time. (High-volume investigator)*

*-- I see no overriding reasons for changing Federal policy. Its presence has kept our IRB "on its toes" more so than would its absence. (Low-volume member)*

*-- The regulations are far too bureaucratic. They specify operational details that do nothing but complicate the process at the expense of the objective. The system would work as well, or better, with much simpler guidelines. (High-volume institution official)*

*-- Our institution performs only behavioral/social research, yet we must comply with regulations designed to cover medical/clinical research. (Low-volume institution official)*

Institution officials and investigators were asked to rate the effect of various Federal requirements, including human subjects protection, in terms of a combination of impact on intended objectives and level of burden to the implementing institution. Investigators were almost twice as likely as institution officials to view human subjects protection requirements as having a high impact on protection while at the same time constituting a low burden to the institution (42 percent and 22 percent, respectively).[33] Alternatively, institution officials were much more likely than investigators to depict the effect of human subjects protection requirements as high impact/high burden (73 percent vs 28 percent, respectively) [IOA5, INC8].

## B. Concerns, Modifications and Other Review Outcomes

The adequacy of protection afforded by an IRB is, in part, a function of the frequency and types of concerns identified through initial review of new protocols and the protocol modifications that ensue. Such concerns and modifications indicate IRBs' "value-add" -- the improvements to protocols that might not have been made without IRB involvement.

### 1. Approved As Submitted

With the expansion and evolution of health research and the inevitable turnover of investigators, the likelihood that human subject research protocols will be deficient in some area of human subjects protection remains high. As such, the rate at which protocols are approved as submitted is a potentially important indicator of adequacy: too high a rate might signal complacency or a lack of due diligence by an IRB. Overall, in 73 percent of IRBs, one-quarter or fewer protocols were approved as submitted [ADB16]. In fact, 34 percent of IRBs did not approve any (zero) protocols as submitted in 1995; 10 percent approved one-quarter to one-half; and 6 percent more than one-half of protocols [CHC2Oa].

### 2. Concerns Raised in Initial Review

*-- [The IRB should] reduce the fanatical obsession with including every risk known to man on the consent form. (Low-volume investigator)*

*-- There seems to be a wide variation across individuals on the IRB as to how much risk is acceptable when the direct benefit to the respondent is small or non-existent. (Low-volume investigator)*

[33]Respondents who said their experience was too limited to form an opinion were excluded from the calculations [INC8].

For protocols submitted in the most recently completed record year (1995), chairs were asked to describe the general frequency of several types of deficiencies in four major areas: consent form, consent process, risk/benefit, and scientific design [CHC17]. The most frequently occurring deficiencies related to consent forms. For example, 60 percent of chairs reported that "language too technical or otherwise unclear" -- the most common consent form concern -- occurred often. (Figure 40) Only a small percentage of chairs indicated the following consent form deficiencies were often identified: risk understated or omitted (11 percent); benefits overstated (8 percent); information on costs omitted (13 percent); and alternatives (with risks and benefits) not described (6 percent).

In the area of consent process concerns, the majority of chairs cited "the circumstances for obtaining consent do not promote comprehension" as a deficiency that was sometimes (52 percent) or often (9 percent) noted. In addition, under scientific design, chairs said the concern that "number of subjects and inclusion criteria may make results equivocal or invalid" sometimes (58 percent) or often (3 percent) arose.

Deficiencies in the area of risk/benefit were least likely to be reported by chairs (compared to the consent form, consent process or scientific design). Two of the most frequent risk/benefit deficiencies identified were "inadequate provision for maintenance of confidentiality" and "inadequate provision for privacy protection", with only 3 percent of chairs indicating these often occurred.

### 3. Protocol Modification

*-- They have not made a single useful change in a protocol. They have slowed projects, and they have required me to "correct" protocols to meet their linguistic standards, which change way too often. (High-volume investigator)*

*--Consent form changes are too often more cosmetic than substantial. (High-volume member*

*-- No problem with the science side, but frustrating delays with "informed consent issues." (Low-volume investigator)*

The likelihood of an investigator modifying his/her protocol, 43 percent overall, was substantially lower (24 percent) for protocols undergoing expedited initial review than for protocols receiving full board initial review (49 percent). In addition, protocols involving invasive mental or physical testing or examination had a 10 percent higher modification rate (50 percent) than all other protocols (40 percent).

Among investigators who indicated the IRB had raised issues that caused modification of their protocol, by far the most common protocol modification was to consent forms, with 78 percent of investigators reporting this modification [INB10]. (Figure 41)

### 4. Conditions on Approval

*-- More recently, approvals have been increasingly issued with required conditions; it is rare to have them [the IRB] merely make a recommendation. This tendency is becoming a source of increasing frustration for many investigators. (High-volume investigator)*

Besides raising concerns and requiring protocol modifications before deciding on approval, IRBs can condition approval by requiring actions like more frequent than annual reporting to the IRB or medical monitoring of subjects. Typically, high-volume IRBs (53 percent) were more likely to take such actions than their low-volume counterparts (27 percent (probably due to the far greater numbers of protocols being reviewed at high-volume IRBs) [CHC16]. At high-volume IRBs, 8 protocols per 100 initial reviews received conditional approval for the action "observed or third

party observation of the research process", while at low-volume IRBs the rate was 4 per 100 protocols. At low-volume IRBs, both "research requiring more than annual reporting" and "observed or required third party observation of the consent process" occurred at a higher rate than at high-volume IRBs. Regarding IRB exclusion category type, a significant difference was observed, with a higher incidence of medical and "mixed" IRBs "reporting more than annually on research protocols", compared to behavioral IRBs, which almost never attached this condition to approval.

#### 5. Actions on Multicenter Protocols

*-- Many IRBs have trouble with NIH-sponsored multi-center studies. NIH guidelines for IRBs seem to be in conflict with NIH-sponsored research. (High-volume administrator)*

*-- I would like to see a federally run "national IRB" which would do initial human subjects reviews of protocols and consent forms for studies with multiple sites. (High-volume member)*

The frequency of actions taken by the IRBs following requests for initial review of multicenter research protocols that originated elsewhere was reported by chairs [CHC20].[34] Fifty-four percent of IRBs required changes in (model) consent forms in one-half or more multicenter protocols. In contrast, only 3 percent of IRBs required changes in the research procedures, and virtually no IRBs disapproved one-half or more of multicenter protocols.

### C. Other IRB Actions

Like opinions on the adequacy of protection and reports on review outcomes, reports of other (non-review) IRB actions such as suspension or termination of approved research indicate the adequacy of protection. Presumably, if these powers were not used occasionally, it might signal that research with inadequate protection was proceeding unchecked. Further, the non-use of these powers in situations where such action was called for would seriously undermine IRB credibility with regard to human subjects protection.

#### 1. Suspension or Termination of Approved Research

For the most recently completed record year, 37 percent of chairs said their IRB had used its authority to suspend or terminate approval of one or more research activities [CHC37]. Among the subgroup of chairs who reported one or more incidences of suspension or termination of research approval, the following precipitating events were identified: failure of investigator to obtain approval for continuation of the study (48 percent of those who noted suspension/ termination); incomplete/inaccurate information provided to the IRB (32 percent); use of research procedures that were not approved by the IRB (27 percent); failure of investigator to obtain informed consent (23 percent); harm to a subject (19 percent); and other (16 percent) [CHC38].

#### 2. Overruling Exemption Determinations

With regard to the percentage of exemption determinations made by investigators or others that were subsequently overruled by the IRB, 41 percent of administrators reported this occurred in fewer than 1 in 20 protocols, while 45 percent indicated that no exemption determinations were overruled [ADB15].

### D. Reports of Potential Problems

Reports of potential problems that might compromise the protection of subjects' rights and welfare was the fourth type of information we used to depict the adequacy of protection.

[34]These figures were estimates in 34 percent of the cases.

### 1. Serious Investigator Non-compliance

For the most recently completed record year, chairs noted the occurrence of five types of serious investigator non-compliance that were reported to/discovered by (one or more incidents) their specific IRB. "Failure to obtain IRB approval to initiate a study" was the form of non-compliance cited most frequently by chairs (33 percent). (Figure 42) The frequency of IRBs that experienced at least one incident of other forms of serious non-compliance was as follows: failure to follow an approved protocol (24 percent); failure to obtain IRB approval to continue a study (more than just tardy submission of continuing/ annual review report) (20 percent); failure to report serious harm to a subject (8 percent). In open-ended comments, chairs indicated a wide variety of other forms of investigator non-compliance, including falsification and undue tardiness [CHC36].

As expected, given the great variation in volume of research overseen among IRBs, the likelihood of a chair reporting serious investigator non-compliance rose as workload increased. While one or more incidences of serious investigator non-compliance were found in 50-80 percent of high-volume IRBs, the percentages for low-volume IRBs ranged from 20 to 45 percent.

When asked to select, based on their opinion, one or more reasons that significantly contributed to the problem of investigators conducting unapproved research, over half of chairs (53 percent) said the investigator was not familiar with the requirement for IRB review. A slightly lower proportion of chairs (46 percent) indicated that the reason was the investigator considered the activity a non-research activity (e.g., innovative treatment, student learning experience) [CHB10].

### 2. Within-Jurisdiction Harms

Forty-four percent of chairs noted that, during the most recently completed record year, their individual IRB had been notified by someone (e.g., a subject, a member of the research team or medical care team, a subject's relative) about a harm to a subject who was within the jurisdiction of the IRB [CHC30]. Based on their knowledge of the past five years, 80 percent of chairs said the number of protocols associated with harms during the most recently completed record year was about the same as during a typical year. The remaining chairs were evenly divided about whether there had been more or less harms than typically occurred [CHC32].

### 3. Legal Actions by Subjects

For the most recently completed record year, the vast majority of institution officials indicated that subjects under the jurisdiction of their specific IRB had neither brought a legal charge or legal claim against the institution and/or IRB (85 percent), nor received compensation from the institution as restitution for research harm, regardless of whether the harm was anticipated and irrespective of whether charges or claims were filed or settled in court (80 percent). Additionally, 60 percent of institution officials said subjects had not received free medical care from the institution as restitution for research harm, while 22 percent indicated they had, and 18 percent did not know the answer to the question [IOB5].

### 4. Subjects' Complaints

When asked to list the most common complaints of human subjects (other than harms), about half of chairs supplied one or more complaints. Compensation complaints accounted for the largest proportion (27 percent), with more than a third of those related to the specific complaint of late payment of subjects. The percentages of chairs

reporting other types of complaints were fairly equally distributed across four categories: lack of information, problems with informed consent, lack of privacy and confidentiality, and miscellaneous concerns like the general inconvenience of study participation [CHC35].

### 5. Informed Consent Process

With regard to who explained and discussed a study and its risks and benefits with subjects or their representatives (if the consent requirement had not been waived for the study), nearly half of investigators said they shared that responsibility with their staff and/or other members of the research team, while nearly a third of investigators reported they alone performed the task [INB27].

In terms of how many minutes were spent by study personnel in explaining and discussing information pertinent to informed consent with a potential subject, investigators indicated a mean of 30 minutes (and a median of 20 minutes) for that activity. Overall, nearly a third of investigators said 10 minutes or less. Regarding high/low-volume differences, investigators from high-volume IRBs noted a mean of 34 minutes spent on discussing information related to informed consent, while those from low-volume IRBs reported a mean of 25 minutes for the same activity [INB28].

### 6. Problems With Investigators

In identifying the types of investigator-related problems that existed for IRBs and the degree to which they affected efficacy of review, 93 percent of chairs and 75 percent of administrators indicated the failure of investigators to initially supply all the information needed to support their request for review was a problem; of these, 31 percent and 12 percent, respectively, termed it a major problem. The failure of investigators to initially provide an acceptable consent form was considered a problem by 88 percent of chairs and 90 percent of administrators, with 15 percent and 30 percent, respectively, considering it a major problem affecting efficacy of review.

With regard to other possible problems with investigators, such as lack of cooperation, circumvention of initial review by casting new studies as amendments to ongoing studies, or attempts to reduce the number of reviews by bundling several distinct studies, the percentages of chairs and administrators who viewed them as actual problems (major and minor) in terms of efficacy of review were substantially lower, ranging from 18 to 26 percent. According to administrators of low-volume IRBs, two problems -- bundling studies and casting new studies as amendments -- were almost nonexistent, while chairs of high-volume IRBs were twice as likely as low-volume IRB chairs to cite these same two problems (probably due to a greater volume of protocols) [CHB8, ADC3].

When asked to what extent, if any, the institution had a problem with investigators initiating research or amending protocols without the required IRB approval, 59 percent of chairs reported it was a minor problem or somewhat of a problem; less than 1 percent each said it was a serious or very serious problem. Additionally, 35 percent of chairs indicated their institutions had not encountered problems of this type [CHB9].

# CHAPTER VI
# ALTERNATIVES AT THE LOCAL AND FEDERAL LEVELS

This chapter discusses ways to improve human subjects protection through changes at both the local and federal levels, based on suggestions from all five categories of respondents. The suggestions were elicited through a mix of closed-end and open-ended survey questions, with the latter garnering a total of 3,179 written comments relative to possible local and federal level changes. Included among these comments were many thoughtful suggestions, some of which are recounted below.

## A. Suggested Changes at the Local Level

Day-to-day participants in human subjects protection -- IRB chairs, members, administrators, institution officials, and investigators -- provided a total of 2,293 written suggestions to an open-ended question about changes at the local level to improve IRBs. Within respondent groups, more than 80 percent of institution officials and chairs (and 60 percent of administrators and investigators) offered specific advice; members were the least likely to comment on local change (54 percent).

Across the five respondent groups, comments fell generally into the categories of: IRB procedures and structures, education and training, additional resources, and a miscellaneous collection of other suggestions. While the responses of chairs, administrators, and institution officials were fairly equally distributed among these categories (15-28 percent in each one), investigators' and members' comments were more likely to target changes in IRB procedures and structures (50 percent and 47 percent, respectively).

Many of the suggested changes in IRB procedures and structures were aimed at streamlining IRB operations, including "more rapid initial screening" (high-volume investigator), "developing a procedure for processing exempt protocols more quickly" (low-volume administrator), "make consent form review less onerous" (low-volume chair), and
establishing "a subcommittee to screen new projects prior to full board meetings" (high-volume member). Other suggestions pertained to improvements in human subjects protection, such as including "more members who are actively engaged in human research" (high-volume institution official), "actively monitoring ongoing studies, especially regarding consent forms" (low-volume investigator), and giving "more attention to the scientific adequacy of protocols" (low-volume member).

With regard to increasing education/training opportunities (e.g., workshops, conferences, and time for professional development), 19 to 24 percent of institution officials, chairs, administrators, and members provided comments. While an overwhelming majority of members (and to a much lesser degree, institution officials) emphasized training and educational opportunities for IRB members, chairs and administrators were more likely to focus on the training of investigators. Interestingly, only 4 percent of investigators commented on changes in education.

Fifteen to 23 percent of institution officials, chairs, and administrators commented on the need for additional resources, while only 7 percent of members and 4 percent of investigators did so. Additional staff -- both professional and clerical -- was the resource most commonly mentioned, with compensation and incentives for chairs, members, consultants and others also receiving considerable attention.

In terms of a miscellaneous collection of other changes, 10 to 28 percent of survey, many of the suggested changes from all five respondent groups had to do with Board members and Board composition. For example, respondents advocated that members have "greater familiarity with social science research in applied settings" (low-volume investigator) and "encourage other than the primary reviewer to critically evaluate protocols" (high-volume chair), and that Boards be more ethnically and racially diverse and include more community/lay members.

The miscellaneous category also included comments from all five groups of respondents on the need for changes related to information technology, with administrators and institution officials being particularly likely to focus on this topic. Suggestions ranged from "computerization for efficient protocol review" (high-volume institution official) to "more access to database technology" (low-volume administrator), "video and computer facilities for the consent procedure" (high-volume chair), and "more attention to the protection of electronic data transmission between study sites and coordinating centers" (low-volume member). In addition, 2 percent of investigators commented on a perceived lack of consistency, calling for IRBs to be "more consistent from study to study" (high-volume investigator) and "more consistent from one month to the next" (low-volume investigator).

In sum, respondents' comments on suggested changes at the local level to improve IRB performance were focused primarily in three areas -- IRB procedures and structure, education and training, and additional resources. As such, these three areas emerged as being the most critical locally in terms of enhancing the quality and efficiency of human subjects protection [CHB14, MBC8, ADC4, IOB11, INC4].

### 1. More on Enhancing IRB Procedures and Structure

Responses to several closed-end questions provided additional insight into the topic of enhancing IRB procedures and structure.

#### a. Top Priorities for More Effort

Chairs, members, administrators**,** and investigators were asked a series of questions designed to elicit their opinions about where greater effort should be focused. The broadest question, which spanned several major IRB functions, was accompanied by two additional questions focused on initial and continuing/annual review. In general, respondents favored the current distribution of effort, offering no strong suggestions relative to changing or refocusing IRB effort.

Across Types of Review

With regard to several major IRB activities -- expedited reviews, full board reviews, and review of FDA required reports of harms to subjects -- the majority of chairs and administrators (excluding those who said the activity was not applicable to local procedures or types of protocols) reported that no change in level of IRB effort was needed [CHB2, ADC2].

For Initial Review

Members and investigators were asked whether less, more, or the same amount of IRB effort should be devoted to various topics during initial review of protocols. Topics included: risk assessment, risk reduction and subject safeguards, elimination of procedures, subject benefits, consent forms, informed consent procedures, scientific design, subject selection, subject recruitment, and other. For each of the topics, the majority of investigators indicated that no change in effort was needed at the time of initial review [INB12]. Thus, investigators passed on the opportunity to report that less effort was needed; by declining, did they reaffirm the reasonableness of the burden associated with IRB initial review? With the exception of one topic, the majority of members also reported that no change in effort was needed. On that topic -- scientific design -- the members who advocated a change in effort were split on whether more or less effort was needed [MBC2].

In a similar question, chairs were asked what their highest priorities would be with regard to topics, if more effort could be devoted to initial review,. Sixty-one percent said more effort was needed, and 22 percent indicated consent forms as the highest priority. Other topics rated as top priorities for more effort in initial review included risk assessment (11 percent), informed consent procedures (9 percent), and scientific design (9 percent) [CHB3].

For Continuing/Annual Review

For each of seven specific topics -- procedures for investigator monitoring of subjects, reports of harms to subjects, use of approved consent form, accrual rate of subjects, number of prospective subjects who refuse participation or withdraw, study findings that may alter risk/benefit balance, and new information in the literature that may alter the risk/benefit balance -- the majority of members indicated that no change in IRB effort was needed at the time of continuing/annual review. However, with regard to four topics, including reports of harms to subjects, number of prospective subjects who refuse participation or withdraw, and study findings or new information in the literature that may alter the risk-benefit balance, a majority of members who said change was needed wanted to see more or much more effort, with percentages ranging from 23 to 38 percent for those who had sufficient experience to form an opinion [MBC3].

In response to a similar question asking chairs to identify their highest priority topic if more effort could be devoted to continuing/annual review, 42 percent of chairs indicated that no additional effort was needed for continuing/annual review [CHB4]. Among chairs in favor of added effort, nearly equal percentages (10 and 11 percent) selected as their top priority topics procedures for investigator monitoring of subjects, demonstrable benefits to subjects or to scientific knowledge from results of study to date, and reports of harms to subjects. Additional choices included: new information in the literature that may alter the balance of risks and benefits, use of approved consent form, number of prospective subjects who refuse participation or withdraw, accrual rate of subjects, and other, with percentages ranging from 8 percent for new information to 2 percent for accrual of subjects.

### b. Strengthening IRB Membership

Chairs and institution officials were asked, if they could strengthen IRB membership, what their highest priorities would be for member qualifications. While chairs were more likely than institution officials to see a need to strengthen IRB membership (73 percent to 58 percent, respectively), both respondent groups rated expertise in particular fields of science as their top priority (22 percent of chairs and 14 percent of institution officials). Community/lay representatives and diversity with regard to race, ethnicity, and/or gender were also evaluated as top priorities by both groups (15 percent and 12 percent, respectively, by chairs, and 9 percent and 10 percent, respectively, by institution officials). In addition, 11 percent of chairs rated expertise in ethics as a top priority qualification, compared to 6 percent of institution officials. Additional selections included: high stature at the institution, expertise in law, and other qualifications [CHB6, IOB7].

### c. Problems with Adjusting IRB Membership

Over half of chairs and institution officials provided written comments on the question of what, if anything, prevented the IRB from adjusting its membership with regard to the top three priority membership qualifications they specified. Both respondent groups
identified search problems, such as locating qualified individuals with specific expertise in priority areas of science, law, and ethics, as a major obstacle to adjusting membership. Additional comments pertained generally to problems with IRB members themselves (e.g., time constraints, lack of interest, competing priorities), as well as features of the IRB member position, including lack of compensation or release time, or to IRB administration issues like “getting members to attend meetings regularly” and “lack of organization at the institution level” [CHB7, IOB8].

### d. Problems with Recruitment and Turnover

When asked whether recruitment and turnover of IRB members and staff created problems that impeded IRB effectiveness, chairs were more likely to report difficulties with recruitment and turnover (too much or too little) of IRB members than staff [CHB5]. With regard to a similar question pertaining to recruitment and turnover of IRB chairs

and members, institution officials also indicated that recruitment and turnover (too much or too little) presented more difficulties relative to members [IOB9].

### 2. More on Education and Training

#### a. The Top Priority for More Effort

When asked to assess whether more or less effort (including that of the chair, members, and administrative staff) should be devoted to seven specific IRB activities, an overwhelming majority of chairs and administrators indicated that more or much more effort is needed in the education of investigators (90 percent and 86 percent, respectively). (Figure 43) Slightly fewer chairs and administrators (77 percent and 76 percent, respectively) said that more or much more effort should go to the education of IRB members and staff [CHB2, ADC2].

#### b. Keeping Up with Human Subjects Protection

During the most recently completed record year, 95 percent of chairs had at some time read a book, journal article, or newsletter related to human subjects protection, and more than half had attended a meeting/workshop on the subject [CHA10]. Members and administrators were nearly equally likely to have read something pertaining to human subjects protection during the previous year (89 percent and 86 percent, respectively), but administrators were much more likely than members to have attended a meeting/workshop on the subject (65 percent versus 16 percent) [MBB3, ADA7].

#### c. Usefulness of References/Resources

Chairs were asked to rate the usefulness in fulfilling their IRB responsibilities of various resources/references. For example, with regard to Federal policy statements and informational sources, including *The Belmont Report*, *OPRR Reports*, *Protecting Human Research Subjects: The IRB Guidebook (OPRR)*, *Protecting Human Subjects* (OPRR videotape), and *FDA Information Sheets*, chairs who were familiar with the resources rated them as somewhat or very useful in 38 to 96 percent of cases. Federal resources embraced by the highest percentages of chairs were *Protecting Human Research Subjects: The IRB Guidebook (OPRR)* and *OPRR Reports*. (Figure 44) The percentages were somewhat lower for journals/newsletters, with 48 and 66 percent of chairs who were familiar with *IRB: A Review of Human Subjects Research* and *Human Research Reports* evaluating them as somewhat or very useful. Members and administrators were asked the same question; of the three respondent groups, members were least likely to be familiar with the various Federal and journal/newsletter resources [CHA9, ADA6, MBB2].

In a different version of the question, investigators were asked to rate the usefulness of various resource/reference items they had utilized, including DHHS Regulations for the Protection of Human Subjects (45CFR46), *The Belmont Report*, model consent form(s) or consent form checklist, protocol content checklist, the institution's human subjects protection guidelines for investigators, or other materials. Of those who had used the specific items, 77 to 95 percent rated them as somewhat or very useful, with the institution's human subjects protection guidelines for investigators and protocol content checklist emerging as the most useful items overall (95 percent and 87 percent, respectively). However, only 43 percent of investigators had used the DHHS Regulations for the Protection of Human Subjects, while a mere 5 percent had used *The Belmont Report* -- the two resources least likely to be employed [INA5].

#### d. Desired Clarification/Guidance by Investigators for HSP Issues

When asked to describe what, if any, human subjects protection issues they wished to receive clarification or guidance on, 19 percent of respondent investigators supplied 144 written responses that fell generally into the following categories: consent, confidentiality, scope of IRB authority, study participants, and other issues.

Twenty-eight percent of comments pertained to consent issues, with 11 percent of total comments targeting consent issues related to children and adolescents. Other requests for clarification or guidance on consent issues were wide ranging, and included consent procedures for indefinite storage of blood samples intended for future DNA analysis.

Confidentiality issues, such as protection of anonymity when medical records are searched and evaluated, accounted for 13 percent of total comments by investigators. Another 13 percent of responses concerned clarification on issues related to study participants, including videotaping of subjects, compensation or other benefits, and referrals if screening uncovers psychological or medical problems. An additional 13 percent of investigators' comments related to more information on the scope of IRB authority, and involved questions such as whether IRB review is necessary for minimal risk research.

A collection of miscellaneous issues accounted for 30 percent of total comments, including: a call for either clarification of terminology and regulations, or guidelines in areas such as ownership of data or the length of time that records must be stored (9 percent); issues of study design (8 percent); and a variety of other concerns, including issues related to biological specimens, requests for information, and liability or harm (11 percent). Three percent of responses pertained to general matters like the overall benefit to society of the IRB process [INC6].

### 3. More on Additional Resources

Top Priorities for New Resources

Among chairs, administrators, and institution officials who said additional IRB resources were needed, clerical staff was the top priority overall, narrowly edging out professional staff and educational and/or training resources. In contrast to administrators and institution officials, a slightly higher percentage of chairs selected professional staff as their top priority over clerical staff. Of the three respondent groups, administrators were the most likely to say that additional resources were needed (92 percent) [CHB1, ADC1, IOB6].

## B. Suggested Changes at the Federal Level

Respondent groups supplied a total of 742 written comments to an open-ended question about changes at the Federal level to improve IRB performance. With overall percentages of comments ranging from highs of 45 percent and 42 percent for administrators and chairs to 22 percent for members and 13 percent for investigators, narrative responses about federal-level changes to improve IRB performance fell largely into five categories. These included: revision/clarification of regulations and IRB practices, other issues relative to regulations and practices, streamlining review, paperwork reduction; and a miscellaneous collection of changes.

Within the category of revision/clarification of regulations/guidelines and practices, investigators and members were the respondent groups most likely to comment (59 percent and 45 percent, respectively), whereas chairs were the least likely to do so (28 percent). Suggested changes relative to clarification included: "clarify the use of videotaping of human subjects" (high-volume investigator), "guidelines to provide consistency in procedures and consents in multi-center studies" (low-volume member), "clarify the IRB role in reviewing adverse events" (high-volume administrator), and "clarify the regulations dealing with cognitively impaired individuals" (high-volume institution official).

Comments pertaining to revisions of existing regulations or practices included the following: "expand the definition of vulnerable subjects to include Alzheimer's and victims of violence" (low-volume chair), "relax the

mandatory inclusion of women and minorities" (low-volume investigator), "revise the insistence on a placebo when the current recognized standard could be used as a control" (high-volume member), "instead of full submission of an Assurance every five years, only require the reporting of changes" (low-volume institution official), and "allow researchers recruiting teenagers to tell them they're being paid" (high-volume investigator).

In the category of other issues relative to regulations and practices, 17 to 20 percent of institution officials, administrators, members, and chairs provided comments; just 10 percent of investigators contributed to this category. Many of the comments pertained to improvements in Federal agency practices, such as "more consistent interpretation of regulations by OPRR" (high-volume chair), "enlarge OPRR staff and use IRB members from across the country to perform site/project visits and reviews (low-volume member), and "better communication between OPRR and IRBs" (high-volume administrator). Other suggestions in this category concerned the creation of new regulations, such as "separate regulations tailored to social science/behavioral research" (low-volume institution official), "guidelines specific to genetic testing" (low-volume administrator), "new rules on adverse events, especially those occurring at outside institutions" (high-volume chair), and "limitations on the role of commercial IRBs" (high-volume administrator).

While 20 to 26 percent of institution officials, administrators, and chairs provided comments relative to streamlining review, members and investigators were less likely to do so, at 11 percent and 5 percent, respectively. Suggestions were wide-ranging, including "full board review by e-mail" (low-volume chair), "drop the requirement to individually address and vote on each protocol receiving continuing review" (high-volume administrator), "require IRB review only after a high NIH score has been received" (high-volume institution official), and "allow written comments from members to count toward a quorum" (low-volume member).

"Fewer trees destroyed by mountains of paperwork" was the general theme of comments in the category of paperwork reduction. Comments were fairly equally distributed among chairs, administrators, and institution officials (12-13 percent); members and investigators were less likely to have provided written responses in this category (8 percent and 5 percent, respectively). Specific suggestions included: "limit the number of revisions and amendments allowed per protocol" (high-volume institution official); "limit the amount of documentation required, especially for meeting minutes" (low-volume administrator), and "reduce the length and detail of consent forms" (low-volume member).

Ten to 14 percent of comments from the respondent groups fell into the category of a miscellaneous collection of federal-level changes to improve IRB performance, with particular emphasis on the topics of centralization/coordination and education. Examples of the former included: "centralized evaluation and review of safety monitoring" (high-volume chair), "Federal certification of IRBs to allow for reciprocity of IRB approvals (high-volume administrator), and "make conflict of interest policies consistent among institutions" (low-volume institution official). Suggestions for education called for Federal agencies to "provide an updated video on human subjects protection" (low-volume institution official), "have OPRR develop a model training program required for all new investigators" (high-volume member), and "provide continuing education in Federal regulations and informed consents" (high-volume investigator).

In sum, while the comments by respondent groups identified five areas that could benefit from changes at the Federal level, the area of greatest interest -- particularly on the part of investigators and members -- concerned revision and clarification of regulations and practices [CHB18, MBC10, ADC6, IOC4, INC11].

### 1. More on Enhancing Regulations and Practices

Responses to several closed-end questions provided additional insight into the topic of enhancing IRB practices and Federal regulations governing IRBs.

### a. Adding Exempt Categories

Eighty-four to 86 percent of institution officials, chairs, and investigators indicated that no additional types of research should be exempt from review. Across the three respondent groups, the suggestions of those who advocated additional categories tended to focus on the following: innocuous, minimal/no risk, or non-invasive research (e.g., questionnaires that contain no sensitive areas, minimal risk behavioral and educational research); research using existing data or specimens, such as chart review or tests done on discarded biological specimens; routine blood draws; and research that is conducted anonymously or without identifiers [CHB15, IOC1, INC9]. Forty-three percent of chairs who wanted additional exempt categories were not fully utilizing existing allowances for exempt research.

### b. Adding Expedited Categories

Nearly equal percentages of chairs and institution officials (76 and 78 percent, respectively) and 87 percent of investigators reported that no additional types of research should be added to the current expedited categories. For those who wanted other expeditable research categories, the most common suggestion concerned various types of research having to do with children. Additional suggestions included research involving existing specimens or tissue samples; research in which manipulation is utilized; and research characterized by respondents as "innocuous," "minimal risk," or "low risk." While chairs and institution officials tended to speak in broader terms about research (e.g., venipuncture, drugs), investigators were apt to use more specific language (e.g., fingerprick, Taxol) [CHB16, IOC2, INC10]. Forty-six percent of chairs that supported additional categories were not fully utilizing exiting options for expeditable research.

### c. Response to Just-in-Time

NIH policy now requires prior IRB review and approval as a condition for NIH scientific review of all applications for funding of nonexempt human subjects research, even though only a fraction will be supported by NIH. One alternative is to require prior IRB review and approval only for applications receiving NIH initial (scientific) review group scores high enough to be considered for funding. Under this alternative, all nonexempt human subjects research would still have prior IRB review and approval as a condition for NIH council review (the second tier of funding decision making); however, the requirement would pertain only to applications whose NIH initial review group scores fell within a pre-specified percentile range.

When asked about the likely results, chairs, members, administrators, and institution officials were about evenly split on "change" or "no change" in IRB review procedures in response to a "just-in-time" alternative [CHB17, MBC9, ADC5, IOC3]. Closely reflecting the opinions of members, administrators and institution officials, a substantial majority of chairs who expect change reported that saved labor would be reapplied to increased efforts in other areas, e.g., initial review of high-risk protocols, as opposed to reducing the total effort applied to IRB responsibilities.

# CHAPTER VII
# THE IRB SYSTEM: WHERE IT'S BEEN, WHERE IT'S GOING

Since the 1960s, Federal policies, guidelines, and regulations for the protection of human subjects have continually evolved, reflecting responses to new concerns and efforts to clarify ambiguities or refine requirements for IRBs and investigators. To keep pace with these ongoing changes in the biomedical and behavioral research environment, particularly with regard to a greatly expanded workload, IRBs have evolved as well. While the current study offers a nationally representative portrait of the IRB system in the mid-1990s, it does not directly address how the system has changed (or not changed) over the intervening decades, and where it is headed in the future. For that, it is instructive to look at prior research relative to the present study (Section A), and at recommendations in the literature and in survey respondents' comments regarding future alterations in the human subjects protection system (Section B). A brief closing note concludes the main body of this report (Section C).

## A. Prior Research

For various methodological reasons (e.g., differences in sampling frames, form of survey questions, etc.), direct comparisons between the present study and major studies of the human subjects protection system carried out in the last two decades cannot be made. However, at a less technical level, comparisons of the findings on like factors do provide clues as to the evolution of the system over time.

### 1. Volume and Characteristics of Human Subjects Research

#### a. Workload Variation

Based on a national evaluation of the IRB system conducted on its behalf by the Institute for Survey Research at the University of Michigan, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research reported in 1978 that IRBs face greatly varying workloads. For example, an IRB at a small institution might not have received even a single proposal in a year, while IRBs in major medical schools received hundreds of proposals for review. As revealed in the present study, uneven distribution of workload continues. The 246 high-volume IRBs performed 88 percent of the yearly total reviews, and the highest volume IRBs accounted for 21 times the number of initial reviews (including exempt, expedited, and full board) conducted in the lowest volume IRBs in this study.

#### b. More About Reviews

According to the probability sample of 61 institutions (drawn from more than 420 institutions with general assurances approved by DHEW) that was the basis for the National Commission study, the average IRB in the late 1970s reviewed 43 proposals per year, with a range extending from 1 to 357 proposals. A survey of 341 chairs performed in 1982 revealed that IRBs reviewed an average of 133 applications per year, and the number of applications reviewed each year by the system as a whole was estimated to be 73,000 (Grunder, 1983). Based on the 491 IRBs in the present study and the 105,000 initial reviews performed, the average per IRB was 214 reviews (if workload variation were not taken into account). As is apparent, the workload continues to increase over time.

#### c. Kinds of Research

According to the National Commission study (1978), nearly two-thirds of the studies reviewed were biomedical, and one-third were behavioral. In the present study, nearly two-thirds of chairs identified clinical research as the most

common kind of science among protocols coming to their IRBs, with behavioral science ranked a distant second (nearly one-fifth), followed by biomedical science, among others.

#### d. Anticipated Risk/Benefit

In the National Commission study, 55 percent of the projects for which information was available were expected by investigators to benefit subjects, and 50 percent of investigators said their projects were either without risk or represented very minimal risk to human subjects. The Advisory Committee on Human Radiation Experiments reported in 1995 that, based on its review, 40-50 percent of human subjects research posed no more than minimal risk of harm to subjects. According to the present study, 56 percent of investigators indicated their protocol would provide a medical benefit for subjects, while less than half said the protocol presented a medical risk (and the majority of those rated the risk as low).

### 2. IRB Personnel and Practices

#### a. Members

In the 1978 National Commission study, the number of IRB members (including chairs) ranged from 5 to 55, with an average of 14, and the majority were biomedical scientists (50 percent) or behavioral scientists (21 percent). According to Grunder (1983), IRBs, on average, were composed of 14 members, 57 percent of whom were from the biomedical sciences. Based on results from the present study, IRB membership ranged from 5 to 44 members, with means of 19.7 and 10.5 members for the highest and lowest decile IRBs, respectively. Members' educations were largely concentrated in the field of clinical sciences (42 percent), followed by fairly equal percentages in the behavioral, biomedical, and social sciences (between 17 to 20 percent).

#### b. Provisions for Exempt and Expedited Review

Given the option of exempting six categories of educational, social, and behavioral research from IRB review or keeping them subject to at least some form of review, such as expedited review, 341 chairs indicated that IRBs had overwhelmingly opted to keep them subject to review (Grunder, 1983). Based on these results, Grunder contended that from the standpoint of the behavioral researcher, the process of review was not much different than it was before the regulations were changed in 1981.

Mishkin (1994) reviewed the operations of about a dozen IRBs and found several serious problems, including confusion about exempt research and expedited review. She
concluded that when an IRB unnecessarily requires exempt research to undergo IRB review (even using expedited review procedures), it imposes burdens on both the principal investigator and the IRB that could be avoided. Conversely, when research that should undergo IRB review (e.g., using previously collected data or tissue from prisoners) is exempted, the rights and welfare of those research subjects are not being protected as required by the regulations.

In the present study, for every exempt and expeditable research category, chairs indicated there were substantial proportions of IRBs -- ranging between 25 and 77 percent, depending on IRB volume and research category -- that choose as standard practice some form of review that was more rigorous than specified by the regulations. chairs reported that about one-half or fewer protocols eligible for exemption were actually exempted from review, depending on research category.

#### c. Educating Members

Fewer than 5 percent of members in the National Commission survey reported receiving any special training with regard to their IRB duties. In terms of new member orientation, 77 percent of members in the present study said they had first learned about what was expected of them as an IRB member in an oral briefing by the IRB chair, staff, or member(s). Other methods for learning about their duties included the specific IRB's handbook or guidelines (62 percent), Federal HSP regulations (52 percent), and other written information on IRBs and research with human subjects (49 percent).

### d. Written Materials for IRB Submission for Initial Review

Approximately one-half of IRBs required proposals to be submitted on standard forms, and most of the others provided investigators with some instruction regarding the submission of proposals (National Commission, 1978). In the present study, administrators reported that all (or nearly all) IRBs required consent forms, IRB review request forms, a summary protocol description and/or a full copy of the protocol.

### e. Assigning Primary or Secondary Reviewers

According to the National Commission survey, about one-half of IRBs assigned proposals to individual members for intensive review. In the present study, 80 percent of IRBs indicated they have adopted the practice of assigning primary and secondary reviewers, who then brought their assessments to the full board review for the larger group to consider.

### f. Number of Meetings

IRBs in the National Commission sample met as few as two and as many as 51 times per year, with an average of 10 meetings per 10-month year. Based on chairs' reports for a recent record year, the frequency of full board meetings ranged from a low of **11** to a high of 50; the median for high-volume IRBs was 15 meetings, compared to 10 for low-volume IRBs.

### g. Investigator Availability During Meetings

In the 1978 study, more than 25 percent of IRBs indicated that investigators always attended meetings at which their proposals were discussed, while more than 80 percent said this happened at least occasionally. Forty-two percent of administrators from low-volume IRBs in the present survey, compared to 17 percent from high-volume IRBs, noted that investigators were routinely encouraged to attend the meetings or to be reachable by telephone.

### h. Greatest Strengths of IRBs

Based on 12 site visits at 10 institutions, a report of the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, entitled *Implementing Human Research Regulations* (1983), commented on the strengths and weaknesses of those IRBs. One of the most frequently mentioned topics was IRB composition, including characteristics of particular members. Among the characteristics mentioned favorably were the expertise, knowledge, and capability of the members, their authority and ability to command respect, their commitment and dedication, the range of issues that the membership was capable of addressing, the rapport among the members, and the diversity and stability of the membership.

In the present study, the majority of chairs and institution officials described various personal characteristics of members -- for example, their work ethic, diversity (of professional backgrounds, race/ethnicity, cultural), commitment to the IRB, and specific expertise -- as the greatest strength of the IRB. Investigators, on the other hand,

were more likely to praise the IRB in terms of the board as a working unit first, and the positive characteristics of individual board members second.

### 3. Reasonable Burden, Sufficient Effort

#### a. Member Effort

IRBs in the National Commission sample spent an average of 760 member-hours per 10-month year on IRB work, with a range extending from 120 to 5,000 member-hours. On average, individual members engaged in 55 hours of review committee work each year, with a range between 17 and 404 hours. Of the estimated total of 516,000 member-hours tallied in the current study, members of IRBs in the highest volume decile reported a mean of 2,128 hours per year, compared to a mean of 294 hours for members in the lowest volume IRBs. On average, individual members at the highest and lowest volume IRBs spent 108 and 28 hours per year, respectively.

#### b. Effort Per Review

According to the National Commission study, the total number of member-hours per proposal (including time spent outside of meetings) averaged 38 hours. In the present study, the average effort per initial review (all IRB personnel) was 7.1 hours for IRBs in the highest volume decile and 14.9 hours for the lowest volume IRB, and the effort expended per continuing/annual review was only about one-seventh as much.

#### c. Meeting Time Per Review

IRBs in the National Commission survey spent an average of almost one hour per proposal in meetings. In a 1996 report on the human subjects protection system, GAO noted that in some cases, due to volume, IRBs spent only 1-2 minutes per review. According to IRB chairs in the present survey, the mean number of meeting minutes per full board initial and expedited initial review was 21.3 and 3.9, respectively. Of course, these numbers are misleading in that they fail to capture the substantially greater amounts of effort spent on review activities prior to the actual meeting, as well as the differences among IRB subgroups.

#### d. Overall Efficiency

The National Commission (1978) found that 98 percent of chairs and members and 95 percent of investigators agreed that the IRB review procedure runs with reasonable efficiency. In the current study, high percentages of chairs and members (87 and 84 percent, respectively) agreed with the statement that "This IRB runs with reasonable efficiency." Investigators were substantially less likely to do so, at 64 percent. However, most of the investigators who did not agree chose the neutral response (on a five-point scale); only a very small proportion (4 percent) strongly disagreed with the statement.

#### e. Getting Into Inappropriate Areas

According to the National Commission survey, 32 percent of chairs and members and 48 percent of investigators agreed that the IRB sometimes got into areas that were not appropriate to its function. Although relatively small percentages of chairs and members (7 and 13 percent, respectively) in the present study agreed with the statement, "This IRB gets into areas that are not appropriate to its function", investigators were more than twice as likely as chairs to answer in the affirmative, at 18 percent.

### 4. Adequacy of Protection

#### a. Rating of Overall Adequacy

Ninety-nine percent of chairs and members and 98 percent of investigators in the 1978 study agreed that IRBs protect the rights and welfare of human subjects, at least to some extent. In the present survey, chairs and members were nearly unanimous in agreeing with the statement that "This IRB protects the rights and welfare of human subjects." With regard to investigators, 83 percent agreed with that statement, including 55 percent who were in strong agreement.

#### b. Effect on Scientific Quality

Findings from the National Commission survey (1978) indicated that 73 percent of chairs and members, and 67 percent of investigators, agreed that the human subjects review procedure had improved the quality of scientific research done at the institution, at least to some extent. However, Goldman and Katz (1982) found that few IRBs consistently examine research designs with much care, and many disapprove projects only when scientific flaws are glaring. Registering a different perspective, Levine (1984) contended that it is not the duty of IRBs to determine the adequacy of research design and methodology, and that IRBs should not accept responsibility for performing functions they are, by design, incompetent to perform. In response, Goldman and Katz (1984) argued it is impossible to make the risk/benefit calculations imbedded in all ethical evaluations of protocols without considering the appropriateness of the research methods and design.

More recently, Kodish et al. (1992) surveyed 32 chairs and 53 investigators and found that nearly equal percentages (91 and 92 percent, respectively) said study design was important in their IRBs. The Advisory Committee on Human Radiation Experiments (1995) stated that if IRBs are to adequately protect the interests of human subjects, they must have the responsibility to determine that the science they approve satisfies some minimal threshold of scientific merit. However, in their own investigation, ACHRE found they were unable to evaluate the scientific merit of a significant number of proposals based on documents submitted by various institutions. The current study revealed that nearly equal majorities of chairs and members (56 and 55 percent, respectively) agreed with the statement, "The scientific quality of research done on human subjects is improved by IRB review," while 37 percent of investigators were in similar agreement.

#### c. Bias/Lack of Expertise

The National Commission study found that 24 percent of chairs and members and 43 percent of investigators agreed that the review committee sometimes makes judgments it is not qualified to make. In its 1996 report, GAO noted that due to the growing complexity of research, IRB members may sometimes lack sufficient understanding of the technical issues to make decisions about the risks and benefits to human subjects. Twenty-one percent of investigators in the present study, compared to 11 percent of members and only 8 percent of chairs, agreed with the statement that "This IRB has difficulty handling some types of research properly because of bias and/or lack of expertise."

#### d. Concerns Raised in Initial Review - Informed Consent

According to the 1978 National Commission study, changes in informed consent were sought in 25 percent of protocols, with investigators indicating that almost all such changes pertained to content rather than the way in which consent was obtained. Hammerschmidt and Keane (1992) noted that readability of consent forms occupied a considerable amount of IRBs' time and attention; however, their research findings demonstrated that no consent form was improved by more than one grade level after IRB review, and forms remained too complex to be understood by most potential subjects.

Faden (1996) observed that consent forms examined by the Advisory Committee on Human Radiation Experiments included incomprehensible scientific or technical language that served to confuse, rather than inform, subjects. According to the GAO report (1996), IRB members devoted a significant portion of meeting time to assessing the adequacy of consent forms (sometimes at the expense of reviewing scientific design). In the present survey, chairs indicated the most frequently occurring protocol deficiencies were related to consent forms. For example, 60 percent of chairs reported the most common consent form concern -- language that was too technical or unclear -- occurred often. Additional consent form deficiencies sometimes or often identified included: risks understated or omitted, benefits overstated, information on cost omitted, and alternatives (with risks and benefits) not described.

### e. Protocol Modifications, Withdrawals, and Rejections

In a one-year period ending in 1975, the University of Michigan survey found that 55 percent of protocols reviewed by IRBs in their sample were modified, while only about 20 out of 2,500 were rejected, and a small additional number were withdrawn. Gray and Cooke (1980) observed that while IRBs frequently require changes in the proposed research (usually involving modifications in the consent form or additional information), they rarely reject proposals. Grunder (1983) reported a similar finding, with about 52 of 133 proposals returned to the investigator for revision or modification, 2 of 133 proposals withdrawn by the investigator, and only one proposal rejected.

Retrospective cross-sectional and longitudinal studies in the 1980s and 1990 have extended and confirmed findings about extremely low rejection rates and a substantial number of protocols that are provisionally approved or deferred until IRB-requested modifications have been made (Chlebowski, 1984; Cleary, 1987; Merton, 1990; Grodin et al., 1986, and Koren & Pastuszak, 1990). In the present study, the likelihood of an investigator modifying his/her protocol -- 43 percent overall -- was substantially lower (24 percent) for protocols undergoing expedited initial review than for protocols receiving full board initial review (49 percent). In addition, protocols involving invasive mental or physical testing or examination had a 10 percent higher modification rate (50 percent) than all other protocols (40 percent).

### f. Serious Investigator Non-Compliance

Over 80 percent of members surveyed in the National Commission study (1978) said it was likely or certain that their IRB would learn of the existence of research involving human subjects that had not been reviewed or was being conducted in a way substantially different from what had been approved by the IRB. In addition, 25 percent of IRBs had become aware of such conduct in the previous year. According to chairs in the present survey, one or more incidences of serious investigator non-compliance were found in 50-80 percent of high-volume IRBs and 20-45 percent of low-volume IRBs, with failure to follow an approved protocol the most often-mentioned infraction.

### g. Within Jurisdiction Harms

At the time of the National Commission study, only half of IRBs had a formal or informal policy with regard to reporting of injuries to subjects within the jurisdiction of the IRB. In most of these, investigators were supposed to notify the IRB; a few IRBs said research was to be halted or reviewed again if injuries occurred. In the current study,

44 percent of chairs noted that, during the most recently completed record year, their individual IRB had been notified by someone (e.g., a subject, a member of the research team or medical care team, a subject's relative) about a harm to a subject who was within the jurisdiction of the IRB.

### h. Primary/Secondary Reviewers and Adequacy of Protection

In reviewing the operations of about 12 IRBs, Mishkin (1994) observed that when an IRB responds to the demands of a heavy workload by appointing one or more members to review and summarize each protocol, the initial review process may be shortchanged; that is, if the primary reviewer does not raise questions or concerns, the IRB often engages in little or no discussion. As a result, the deliberative process -- one of the primary purposes of the IRB -- is supplanted by the need to keep up with an ever-increasing workload. Similarly, the 1996 GAO report maintained that when primary reviewers (one, two, or several) are assigned to comprehensively examine a study in advance of a meeting, other members tend to rely on the conclusions of the primary reviewer(s), and are therefore less prepared to identify and discuss potential problems.

### i. Staff Participation in Continuing/Annual Review

Mishkin (1994) noted that one of the most frequent and troublesome problems in terms of IRB operations was the lack of substantive IRB review at the time of annual renewals. Due to heavy IRB workloads, administrative staff are often assigned the task of reviewing reports to assure that filing has taken place and all spaces are filled in on the form. According to Mishkin, this task was sometimes adequately performed and sometimes not. After staff had "approved" the application for renewal, it might be submitted to the IRB with several other renewals and approved without discussion at the meeting. In such instances, approval had taken place with no substantive review by the IRB or even by a knowledgeable member. In Mishkin's view, that constitutes a violation of the regulations, and may expose human subjects to risks for which they have received no information.

Along these same lines, the GAO report (1996) voiced concerns about the continuing/annual review process, including the superficiality of the reviews (if performed at all), and the fact that in some cases, administrative staff without scientific expertise reviewed continuing/annual review forms, and did so only to ensure that all information had been provided.

### j. Inconsistency Within and Among IRBs

In a controversial study in which 3 hypothetical protocols were reviewed by 22 IRBs that knew they were participants, Goldman and Katz (1982) found substantial inconsistencies within and among IRBs regarding standards for review, approval or disapproval of protocols, and reasons for the types of decisions that were made. While consistency among IRBs is not, per se, an assurance of good judgment making, Goldman and Katz asserted that standards embodied in federal regulations regarding IRBs and standards for the appropriateness of research design and method should not vary across communities or within individual IRBs. They concluded that while the peer review process might be ineffective in detecting specific abuses, it may prevent many abuses from appearing in protocols by creating an awareness of the ethical implications of conducting research on human subjects.

According to Veatch (1982), the inconsistencies found in the above study suggested that patients and other research subjects were at the mercy of random variation within and among IRBs. He said that while institutions in a pluralistic society should be permitted to hold varying sets of values, it was hard to see why subjects in a given community should receive varying degrees of protection of their rights and welfare as a function of they institution they happened to choose or were sent to.

Eaton (1983) studied 111 proposals reviewed by experienced researchers and found that researchers were in agreement only 8 percent of the time regarding the appropriateness of the proposals for use with human subjects. A similar lack of agreement was discovered by Doob (1983), who sent out 1 of 9 sample research proposals to each of 375 universities in the United States. Results indicated that the same type of proposal, involving the same level of violation, often was approved at one institution but not another, sometimes even within two institutions in the same community. Doob concluded that the approval of a proposal, especially a socially sensitive one, was sometimes a matter of luck, such as where the researcher was working when the proposal was submitted. However, he questioned whether consistency among IRBs was inherently desirable, arguing instead that because members were selected to represent different community values, a diversity of opinions about the acceptability of research for use with human subjects was not only inevitable but desirable, and high levels of agreement within an IRB might indicate an inadequate sampling of views.

Prentice and Antonson (1987) reported that members and investigators were generally aware that one of the most significant problems faced by IRBs is inconsistency in the protocol review process. Despite various factors that influenced protocol decisions (e.g., institutional values and pressures, board attendance, the number of ethically difficult protocols, ambiguity of federal regulations) and the different formats employed for protocol reviews across institutions, Prentice and Antonson contended that the basic principles underlying IRB review should remain constant, thus serving to minimize inconsistency.

Kodish et al. (1992) observed that IRBs were deliberately created to serve as local review bodies and consequently are permitted flexibility and discretion in reaching their conclusions, even though some commentators have noted that such flexibility can result in inconsistent decisions from one IRB to another. According to Lind (1992), the possibility of consistency at the national level, reached through a coordinated discussion of challenging concepts, is limited by the decentralized nature of IRBs that allows local rather than federal values to determine many issues. A more recent article in the *Journal of the American Medical Association* (1996) asserted that irregularity among IRBs can be a plus to the extent it reflects an appeal to local understanding and values. However, the reasons for such diversity need to be understood, and methods developed for identifying error or prejudice and correcting irregularities due to bias.

Although the present study did not specifically address issues related to the consistency (or lack thereof) of protocol reviews within and among IRBs, this area obviously merits further attention. A question raised by Goldman and Katz in 1982 remains pertinent today: Is consistency in IRB review desirable and a good criterion for the effectiveness of individual IRBs or the system as a whole, given the diversity of IRB membership and the decentralized nature of IRB functions?

## B. Suggestions for Altering the Human Subjects Protection System

The government and the research community, whose ultimate goal is the advancement of scientific knowledge, struggle to balance two sometimes competing objectives -- the need to protect research subjects from avoidable harm and the desire to minimize the regulatory burden on research institutions and their individual scientists. All things considered, this balance appears to have been achieved, and most people involved with research or IRB activities believe that the current system for protecting the rights and interests of human research subjects is working well. That is not to say, however, that the system is without flaws, as evidenced by the array of suggested improvements offered in the recent literature and by survey respondents in the present study. In general, these comments focused on changes in: IRB operations, oversight of the human subjects protection system, and education and training.

### 1. Changes in IRB Operations

A reduction in workload was the focus of many changes relative to IRB operations suggested in the literature. According to a 1996 article in the *Journal of the American Medical Association*, possible strategies include:

- Reviewing protocols only after funding decisions are made, since IRBs currently spend about half their time reviewing proposals that ultimately are not funded.

- Expanding the use of expedited review to cover additional areas, such as annual reapprovals and amendments to protocols submitted within the period of approval for the protocol.

- Decreasing excessive and nonproductive paperwork by, for example, limiting the reporting requirement for adverse events to only those events that are serious and unanticipated.

- Doubling IRB effort by splitting IRBs into two (or more) individual IRBs or by establishing additional IRBs with the same administrative structure or chair for continuity of effort.

- Paying for work, in the form of academic "credit" or reimbursement, in order to attract and keep members on IRBs.

- Outsourcing the work through contracts with independent IRBs established as for-profit consultation ventures to deal with noninstitution-based research projects.

- Computerizing IRBs and research offices to relieve the paperwork load**.**

Across the five groups surveyed in the present study, respondents' suggestions for changes in IRB operations included all of the above. Additional comments pertained to ways of streamlining operations, including "pre-screening protocols at the departmental or unit level" (high-volume chair), "allowing oral presentations to the IRB if major modifications are required after initial review of a protocol" (high-volume investigator), "spending less time on changing the semantics of protocols" (low-volume member), and "showing more sensitivity to disciplines that do not follow the standard model for scientific research" (high-volume member). Other suggestions relative to IRB operations centered on improvements in human subjects protection, such as "including more members who are actively engaged in human research" (high-volume institution official) and " enforcing the requirements, because some research slips past" (low-volume investigator). To enhance IRB operations, additional resources were called for, with supplemental staff being the most frequently mentioned.

### 2. Changes in Oversight

In response to concerns about irregularities -- for example, wide variations in the quality of IRB reviews, the lack of checks and balances with regard to regulatory compliance, and possible compromises in the independence of IRB reviews due to factors such as close collegial ties between investigators submitting protocols to the IRB and IRB members, pressures from institution officials to attract and retain government or corporate research funding, and the reluctance to criticize studies conducted by leading scientists -- the current literature contains many suggestions for strengthening the oversight of IRBs and researchers. These include:

- Periodically evaluating the entire system of rules and procedures for protecting human research participants, in part to ensure that the system of sanctions provided for in the Common Rule functions adequately.

- Extending the scope of human subjects protection to areas of research that are conducted largely independent of federal funding (e.g., some research on reproductive technologies).

- Increasing the effectiveness of the oversight mechanism for ensuring compliance by investigators and IRBs through random samples of protocols from all types of research settings, including interviews with the subjects of the research, and through random site visits to IRBs by federal agencies (possibly carried out by consultants to offset the increase in workload).

- As biomedical science becomes more entrepreneurial, specifying the limits on researchers and institutions that are simultaneously financially invested in the development of products and in the testing of those products.

- Including in the IRB process experts from scientific groups outside the institution, particularly in the case of high-volume IRBs, and quasi-professionalizing the role of outside members, linking them in groups that could come together to study common issues and perhaps give greater uniformity to concepts like minimum risk.

- Developing a process by which IRB decisions can be appealed, and errors or prejudices that entered into decisionmaking identified and corrected.

Comments by survey respondents pertaining to changes in the oversight system included calls to: "enlarge OPRR staff and use IRB members from across the country to perform site/project visits and reviews" (low-volume member); "hold institutions accountable for oversight, monitoring, and education" (high-volume chair); "create a mechanism to ensure that all research with human subjects is reported to IRBs" (low-volume investigator); and "make conflict-of-interest policies consistent among institutions" (low-volume institution official). However, some respondents took the opposite tack with recommendations to: "loosen regulations that leave IRBs paralyzed with fear" (low-volume investigator), "downshift the increasingly bureaucratic attitude" (high-volume chair), and "relax requirements so as not to stifle research" (low-volume investigator). Overall, survey respondents were much more concerned with revising and clarifying present regulations and practices relative to oversight than with establishing new regulatory requirements.

One final note: in its 1996 report on the human subjects protection system, GAO declared that "Finding the balance between that extreme [continuous on-site inspections of every research institution and its studies] and a process that relies almost exclusively on paper reviews is the fundamental challenge facing regulators and IRBs in the current HHS oversight system."

### 3. Changes in Education and Training

Survey respondents voiced many requests for improvements in the education and training of IRB members, staff, and researchers at both the local and federal levels through workshops, conferences, educational resources and materials, and more time for professional development. Specific suggestions included "offering seminars frequently to new faculty and graduate students to orient them to guidelines and filling out forms" (low-volume investigator); "more education regarding federal policy for principal investigators and IRB members (high-volume chair); "new methods for keeping members and investigators up to date on regulations and developments" (high-volume institution official); and "required new member orientation" (low-volume institution official). In addition, the many requests from survey respondents for clarification and guidance on a wide array of existing regulations, procedures, and practices can be viewed, at least in part, as pleas for further education in those areas.

Education was also a major topic of interest for the Advisory Committee on Human Radiation Experiments (1995), which emphasized the training of biomedical scientists, particularly with regard to ethics. The ACHRE report noted that many IRB chairs perceive researchers and administrators as having an insufficient appreciation for the ethical dimensions of research involving human subjects and the importance of the work of IRBs. However, without an appreciation of the moral aspects of human subjects research and the value of institutional oversight, the rights and interests of research subjects cannot be protected; and necessary changes in attitudes are not likely to occur through strengthening federal rules and regulations or developing harsher penalties. Therefore, it is essential that medical colleges and researchers make ethical considerations central to the conduct of research, so that future scientists have a clear understanding of their duties to human subjects, and a clear expectation that the leaders of their fields value good ethics as much as they value good science.

Of equal importance, according to ACHRE, is the development of a more common understanding among the public of research involving human subjects, its purposes, and its limitations. As the report observes, "Some of what is regrettable about the past happened, at least in part, because we as citizens let it happen." By educating the public, as well as those in the research community, about human subjects protection, the likelihood of future abuses will be further diminished.

## C. Closing Note

Past abuses triggered the development and implementation of a human subjects protection system that, by all accounts, appears to have functioned effectively in the intervening decades since the last national-level study. Thus, despite rapid changes in the biomedical environment and a steadily escalating workload, it appears the institutional review board system has continued to ensure that human research subjects are adequately protected from undue risk and endangerment. While the system is by no means perfect and will continue to undergo modification, its track record to date inspires considerable confidence that the protection of human research subjects will be adequate and ongoing for the foreseeable future.